STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 14[illegible]3

TO:	From:
Andrew D Kosar Location: REM/3C04/3C18 Art Unit: 1654 Thursday, March 10, 2005 Case Serial Number: 10/075097	Alex Waclawiw Location: Biotech-Chem Library Rem 1A71 Phone: 272-2534 Alexandra.waclawiw@uspto.gov

Search Notes

Examiner Kosar,

In many cases these kinds of peptides are not structurally searchable. I searched it as a structure and also using derivatives of PEG and Insulin. If you would like for me to try something else, please let me know.

Alex Waclawiw

Access DB# 144813

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Andrew D. Kosar Examiner# : 80341 Date: 3/4/05

Art Unit: 1654 Phone Number: (571)272-0913 Serial Number: 10/075,097

Mail Box and Bldg/Room Location: Mail: REM 3c18 Results Format Preferred (circle): Paper Disk E-mail
Office: REM 3c04

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: METHODS OF TREATING DIABETES MELLITUS

Inventors (please provide full names): **Ekwuribe, Nnochiri N.; Price, Christopher H.; Still, James Gordon; Filbey, Jennifer Ann.**

Earliest Priority Filing Date: 2/15/2001 (US provisional)

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following claims:

Please see the attached method claim.

PP 20

46

****

STAFF USE ONLY

Searcher: Alexandra Waclawiw
Searcher Phone: Technical Info. Specialist CM1-6A02 Tel: 308-4470
Searcher Location:
Date Searcher Picked Up: 3-10
Date Completed: 3-10
Searcher Prep & Review Time: 20
Clerical Prep Time:
Online Time: 46

Type of search

NA Sequence (#)
AA Sequence (#)
Structure (#) &
Bibliographic 4
Litigation
Full Text
Patent Family
Other

Vendors and cost where applicable

STN 351
Dialog
Questel/Orbit
Dr. Link
Lexis/Nexis
Sequence System
WWW/Internet
Other (specify)

14. (Previously Presented) A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

1-24 1-4

wherein:

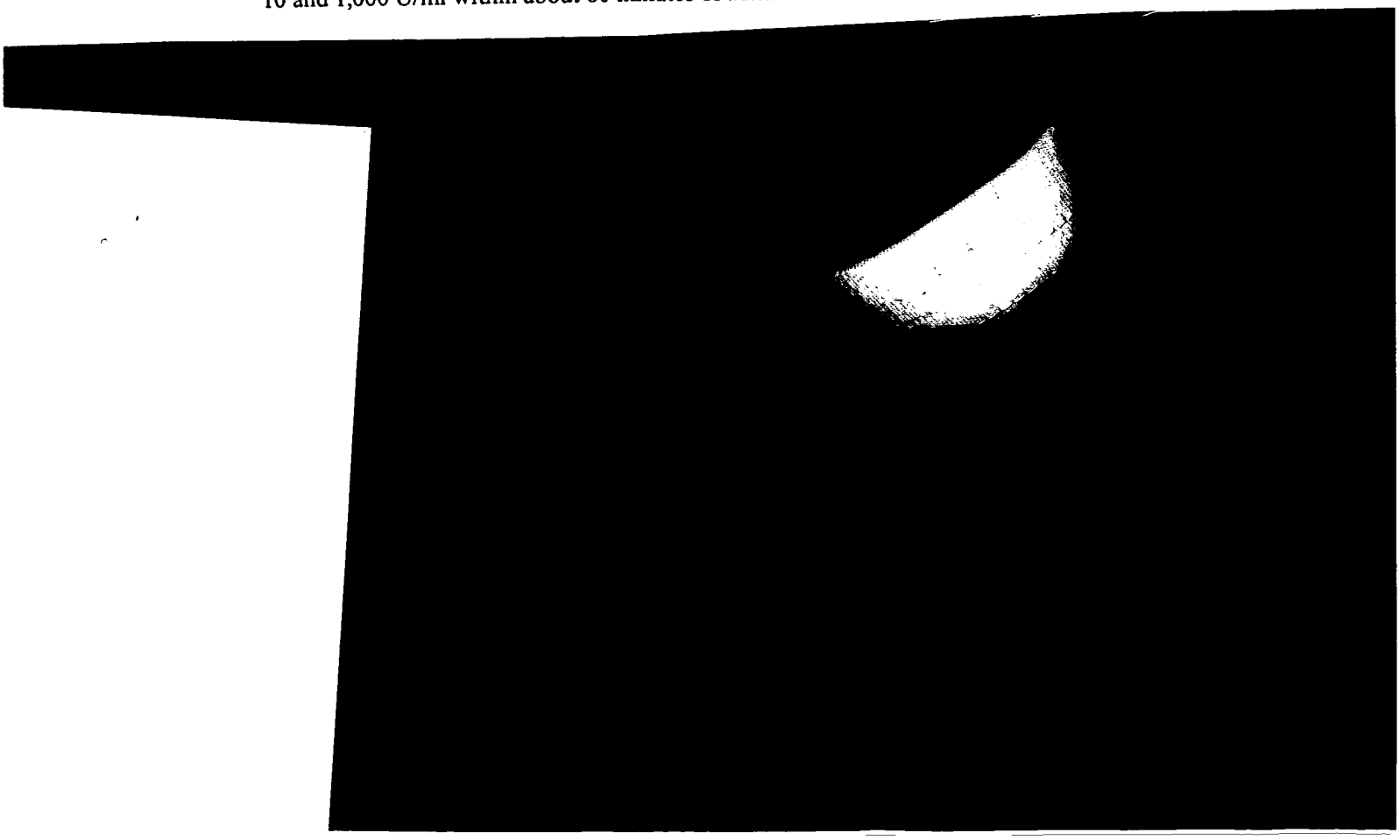
X is a moiety which forms an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the conjugate of Formula III is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.



```
=> fil reg
FILE 'REGISTRY' ENTERED AT 14:02:18 ON 10 MAR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    9 MAR 2005  HIGHEST RN 844817-50-1
DICTIONARY FILE UPDATES:   9 MAR 2005  HIGHEST RN 844817-50-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l 14
'L' IS NOT VALID HERE

=> d que l4
L1          7728 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN
L2          5862 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND PS/FS
L3         99073 SEA FILE=REGISTRY ABB=ON  PLU=ON  C2H4O
L4             7 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 AND L3
```

} insulin seq's with PEG (C_2H_4O) in structure.

```
=> d l4 1-7

L4   ANSWER 1 OF 7  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   100040-03-7  REGISTRY
CN   Poly(oxy-1,2-ethanediyl), α-ethyl-ω-hydroxy-, 30B-ester
     with insulin (human) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   3,4,44,45,90,91-Hexathia-8,11,14,17,20,23,26,29,32,35,38,41,48,51,54,57,60
     ,63,66,69,72,75,78,81,84,86-hexacosaazabicyclo[72.11.7]dononacontane,
     cyclic peptide deriv.
CN   Insulin (human), poly(oxy-1,2-ethanediyl) deriv.
CN   Insulin (ox), 8A-L-threonine-10A-L-isoleucine-30B-L-threonine-,
     poly(oxy-1,2-ethanediyl) deriv.
CN   Poly(oxy-1,2-ethanediyl), α-ethyl-ω-hydroxy-, 30B-ester
     with 8A-L-threonine-10A-L-isoleucine-30B-L-threonineinsulin (ox)
FS   PROTEIN SEQUENCE
MF   (C2 H4 O)n C259 H387 N65 O77 S6
CI   PMS, MAN
PCT  Manual registration
SR   CA
LC   STN Files:   CA, CAPLUS
DT.CA  CAplus document type:  Patent
RL.P   Roles from patents:  RACT (Reactant or reagent)

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
```

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 92090-71-6 REGISTRY
CN Poly(oxy-1,2-ethanediyl), α-[[[4-[7-[[[1-[5,35-bis[[4-[[[(2-chlorophenyl)methoxy]carbonyl]oxy]phenyl]methyl]-17-[3-[[imino[[(4-methoxyphenyl)sulfonyl]amino]methyl]amino]propyl]-41,60,60-trimethyl-29,47-bis(1-methylethyl)-26-[[(1-methylethyl)dithio]methyl]-32,38,50-tris(2-methylpropyl)-1,4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58-eicosaoxo-20,44-bis[3-oxo-3-(phenylmethoxy)propyl]-2-[1-(phenylmethoxy)ethyl]-56-[(phenylmethoxy)methyl]-8,11-bis(phenylmethyl)-53-[[1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-59-oxa-3,6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54,57-nonadecaazahenhexacont-1-yl]-2-pyrrolidinyl]carbonyl]amino]-15-(2-bromophenyl)-4-methyl-3,6,13-trioxo-2,14-dioxa-5,12-diazapentadec-1-yl]-2-nitrobenzoyl]amino]acetyl]-ω-hydroxy-, stereoisomer (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Insulin (ox-B reduced), 1-de-L-phenylalanine-2-de-L-valine-3-de-L-asparagine-4-de-L-glutamine-5-de-L-histidine-6-de-L-leucine-7-de-L-cysteine-8-deglycine-9-[N-[(1,1-dimethylethoxy)carbonyl]-O-(phenylmethyl)-L-serine]-10-[1-(triphenylmethyl)-L-histidine]-19-[3-[(1-methylethyl)dithio]-L-alanine]-22-[N5-[imino[[(4-methoxyphenyl)sulfonyl]amino]methyl]-L-ornithine]-27-[O-(phenylmethyl)-L-threonine]-29-[N6-[[(2-bromophenyl)methoxy]carbonyl]-L-lysine]-, poly(oxy-1,2-ethanediyl) deriv.**
FS PROTEIN SEQUENCE
MF **(C2 H4 O)n C213 H255 Br Cl2 N30 O47 S3**
CI PMS, MAN
PCT Manual registration
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 85875-23-6 REGISTRY
CN **Insulin (swine), NB-(hydroxyacetyl)-, NB-ether with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,4,44,45,90,91-Hexathia-8,11,14,17,20,23,26,29,32,35,38,41,48,51,54,57,60,63,66,69,72,75,78,81,84,86-hexacosaazabicyclo[72.11.7]dononacontane, cyclic peptide deriv.
CN **Insulin (ox), NB-(hydroxyacetyl)-8A-L-threonine-10A-L-isoleucine-, NB-ether with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl)**
FS PROTEIN SEQUENCE
MF **(C2 H4 O)n C258 H385 N65 O78 S6**
CI PMS, MAN
PCT Manual registration
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 85875-22-5 REGISTRY
CN **Insulin (swine), NB-(hydroxyacetyl)-29B-[N6-(hydroxyacetyl)-L-lysine]-, NB,29B-diether with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,4,44,45,90,91-Hexathia-8,11,14,17,20,23,26,29,32,35,38,41,48,51,54,57,60,63,66,69,72,75,78,81,84,86-hexacosaazabicyclo[72.11.7]dononacontane, cyclic peptide deriv.
CN **Insulin (ox), NB-(hydroxyacetyl)-8A-L-threonine-10A-L-isoleucine-29B-[N6-(hydroxyacetyl)-L-lysine]-, NB,29B-diether with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl)**
FS PROTEIN SEQUENCE
MF **(C2 H4 O)n (C2 H4 O)n C261 H389 N65 O80 S6**
CI PMS, MAN
PCT Manual registration
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 78337-41-4 REGISTRY
CN **Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, NB-ester with NB-[[(6-carboxyhexyl)amino]carbonyl]insulin (swine) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,4,44,45,90,91-Hexathia-8,11,14,17,20,23,26,29,32,35,38,41,48,51,54,57,60,63,66,69,72,75,78,81,84,86-hexacosaazabicyclo[72.11.7]dononacontane, cyclic peptide deriv.
CN **Insulin (ox), NB-[[(6-carboxyhexyl)amino]carbonyl]-8A-L-threonine-10A-L-isoleucine-, NB-ester with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl)**
CN **Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, NB-ester with NB-[[(6-carboxyhexyl)amino]carbonyl]-8A-L-threonine-10A-L-isoleucineinsulin (ox)**
FS PROTEIN SEQUENCE
MF **(C2 H4 O)n C265 H396 N66 O79 S6**
CI PMS, MAN
PCT Manual registration
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 78337-40-3 REGISTRY
CN **Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, NB-ester with NB-[[[6-(carboxyamino)hexyl]amino]carbonyl]insulin (cattle) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,4,44,45,90,91-Hexathia-8,11,14,17,20,23,26,29,32,35,38,41,48,51,54,57,60,63,66,69,72,75,78,81,84,86-hexacosaazabicyclo[72.11.7]dononacontane, cyclic peptide deriv.
CN **Insulin (ox), NB-[[[6-(carboxyamino)hexyl]amino]carbonyl]-, NB-ester with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl) (9CI)**
CN **Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, NB-ester with NB-[[[6-(carboxyamino)hexyl]amino]carbonyl]insulin (ox)**
FS PROTEIN SEQUENCE
MF **(C2 H4 O)n C263 H393 N67 O78 S6**
CI PMS, MAN
PCT Manual registration
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L4 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 70815-57-5 REGISTRY
CN **Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, 7,19-diester with 7-[S-(4-carboxy-2,6-dinitrophenyl)-L-cysteine]-19-[S-(4-carboxy-2,6-dinitrophenyl)-L-cysteine]insulin (cattle-B reduced) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, 7,19-diester with 7-[S-(4-carboxy-2,6-dinitrophenyl)-L-cysteine]-19-[S-(4-carboxy-2,6-dinitrophenyl)-L-cysteine]insulin (ox-B reduced)**
FS PROTEIN SEQUENCE
MF **(C2 H4 O)n (C2 H4 O)n C171 H236 N44 O53 S2**
CI PMS, MAN
PCT Manual registration
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 14:02:48 ON 10 MAR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 10 Mar 2005 VOL 142 ISS 11
FILE LAST UPDATED: 9 Mar 2005 (20050309/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

```
=> d que nos l10
L1          7728 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN
L2          5862 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND PS/FS
L3         99073 SEA FILE=REGISTRY ABB=ON  PLU=ON  C2H4O
L4             7 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 AND L3
L10            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4


=> d .ca l10 1-5

L10  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1986:69169  HCAPLUS
DOCUMENT NUMBER:          104:69169
TITLE:                    Insulin derivatives modified in the B30 position for
                          treating diabetes mellitus
INVENTOR(S):              Grau, Ulrich; Geiger, Rolf; Obermeier, Rainer
PATENT ASSIGNEE(S):       Hoechst A.-G. , Fed. Rep. Ger.
SOURCE:                   Ger. Offen., 29 pp.
                          CODEN: GWXXBX
DOCUMENT TYPE:            Patent
LANGUAGE:                 German
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     DE 3334407            A1    19850404    DE 1983-3334407         19830923
     EP 137361             A2    19850417    EP 1984-111058          19840917
     EP 137361             A3    19870506
     EP 137361             B1    19900516
         R:  AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE
     HU 36843              A2    19851028    HU 1984-3491            19840917
     AT 52791              E     19900615    AT 1984-111058          19840917
     FI 8403695            A     19850324    FI 1984-3695            19840920
     DK 8404530            A     19850324    DK 1984-4530            19840921
     DK 172632             B1    19990322
```

NO 8403799	A	19850325	NO 1984-3799		19840921
AU 8433419	A1	19850328	AU 1984-33419		19840921
AU 573624	B2	19880616			
JP 60094999	A2	19850528	JP 1984-196962		19840921
ZA 8407440	A	19850529	ZA 1984-7440		19840921
ES 536115	A1	19850601	ES 1984-536115		19840921
CA 1247545	A1	19881227	CA 1984-463810		19840921
IL 73021	A1	19890910	IL 1984-73021		19840921
PRIORITY APPLN. INFO.:			DE 1983-3334407	A	19830923
			EP 1984-111058	A	19840917

ED Entered STN: 08 Mar 1986

AB Bovine, swine, or human insulin derivs. esterified or amidated in the B-30 position were prepared either by condensing a protected des-B23-30-octapeptide insulin with protected H-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-R30-R31 (R30 = genetically codable L-amino acid residue, R31 = substituted amino, alkoxy, etc.), or by treating a Des-(B30)-insulin with H-R30-R31. Thus, treating swine insulin with [(tert-butoxycarbonyl)oxy]succinimide in DMF/Me2SO containing N-ethylmorpholine at room temperature for 6 h, incubating the product with trypsin at 36°, dissolving the resulting 3.25 g NαA1,NαB1-bis-BOC-des-(B23-30)-octapeptide insulin (swine) (BOC = Me3CO2C) along with 100 mg 1-hydroxybenzotriazole, 750 mg HCl.gly-Ph-Phe-Tyr(But)-Thr-Pro-Lys(BOC)-Thr(But)-OPr, and 0.5 mL N-ethylmorpholine in DMF, treating the reaction mixture with dicyclohexylcarbodiimide for 24 h, reacting the product (still protected) with 5 mL F3CCO2H and 1 mL anisole at room temperature for 60 min, and purification of the product using 10% HOAc over SephadexR G50 or G75 gave 1.2 g human insulin-(B30)-OPr. Pharmaceuticals containing swine-(B30)-OMe, human insulin ArgB31-OH, etc., were bioassayed.

IC ICM C07C103-52
ICS A61K037-26

CC 34-4 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63

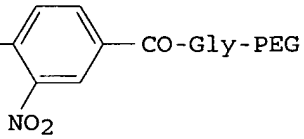
IT 76688-23-8 80449-79-2 81959-12-8 96351-10-9 **100040-03-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(insulin activity of)

L10 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	1984:552305 HCAPLUS
DOCUMENT NUMBER:	101:152305
TITLE:	Synthesis of the C-terminal undeca- and protected docosapeptide of bovine insulin B-chain
AUTHOR(S):	Hemmasi, Bahram; Stueber, Werner; Bayer, Ernst
CORPORATE SOURCE:	Inst. Org. Chem., Univ. Tuebingen, Tuebingen, D-7400, Fed. Rep. Ger.
SOURCE:	Hoppe-Seyler's Zeitschrift fuer Physiologische Chemie (1984), 365(4), 485-92 CODEN: HSZPAZ; ISSN: 0018-4888
DOCUMENT TYPE:	Journal
LANGUAGE:	English

ED Entered STN: 27 Oct 1984

GI

R= 

AB Title undecapeptide H-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-Ala-OH (I) (B20-30) and title protected docosapeptide Boc-Ser(CH2Ph)-His(CPh3)-Leu-Val-Glu(OCH2Ph)-Ala-Leu-Tyr(ZCl-o)-Leu-Val-Cys(SCHMe2)-Gly-Glu(OCH2Ph)-Arg(Mps)-Gly-Phe-Phe-Tyr(ZCl-o)-Thr(CH2Ph)-Pro-Lys(ZBr-o)-Ala-OH (II; Boc = Me3CO2C, ZCl-o = CO2CH2C6H4Cl-o, Mps = p-MeOC6H4SO2, ZBr-o = CO2CH2C6H4Br-o) (B9-30) were prepared by the liquid-phase method using nitrobenzoylglycyl-poly(oxyethylene) as the soluble support. Thus, Boc-Ala-OR [PEG = poly(oxyethylene)] was extended to Boc-Gly-Glu(OCH2Ph)-Arg(Mps)-Gly-Phe-Phe-Tyr(ZCl-o)-Thr(CH2Ph)-Pro-Lys(ZBr-o)-Ala-OR1 (III, R1 = R) (IV) by stepwise peptide couplings, and IV was cleaved by irradiation in Me2SO to give III (R1 = H), which was deblocked by HF/anisole to give I. II was prepared from IV. Racemization tests indicated that no residue was significantly racemized.
CC 34-3 (Amino Acids, Peptides, and Proteins)
IT 91987-24-5P 91987-25-6P **92090-71-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and photolytic cleavage of)

L10 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:215966 HCAPLUS
DOCUMENT NUMBER: 98:215966
TITLE: Synthesis and spectroscopic characterization of insulin derivatives containing one or two poly(ethylene oxide) chains at specific positions
AUTHOR(S): Ehrat, M.; Luisi, P. L.
CORPORATE SOURCE: Tech.-Chem. Lab., ETH-Zent., Zurich, 8092, Switz.
SOURCE: Biopolymers (1983), 22(1), 569-73
CODEN: BIPMAA; ISSN: 0006-3525
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
AB Poly(ethylene oxide) (PEO) Me ether was converted to MeO(CH2CH2O)nCH2CO2H, which was condensed with NA1, NB29-Msc2-insulin (Msc = MeSO2CH2CH2O2C) and NA1-Msc-insulin and the resulting protected products were Msc-deblocked to give the corresponding NB1-PEO- and NB1,NB29-PEO2-modified insulins. The CD spectra of the latter PEO-modified insulins were altered from that of insulin.
CC 34-3 (Amino Acids, Peptides, and Proteins)
IT 9004-10-8DP, poly(ethylene glycol)-modified derivs. 25322-68-3DP, insulin derivs. **85875-22-5P 85875-23-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and CD of)

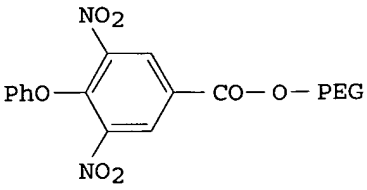
L10 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1981:443673 HCAPLUS
DOCUMENT NUMBER: 95:43673
TITLE: Insulin derivatives
INVENTOR(S): Obermeier, Rainer; Uhmann, Rainer; Summ, Hans Dieter; Regitz, Guenter; Geisen, Karl
PATENT ASSIGNEE(S): Hoechst A.-G., Fed. Rep. Ger.
SOURCE: Ger. Offen., 13 pp.

CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

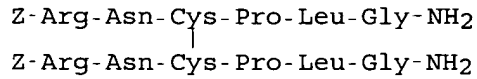
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2930542	A1	19810212	DE 1979-2930542	19790727
EP 27161	A1	19810422	EP 1980-104267	19800719
EP 27161	B1	19830427		
R: AT, BE, CH, DE, FR, GB, IT, NL, SE				
AT 3145	E	19830515	AT 1980-104267	19800719
ES 493550	A1	19810416	ES 1980-493550	19800721
DK 8003243	A	19810128	DK 1980-3243	19800725
JP 56022326	A2	19810302	JP 1980-101370	19800725
CA 1156217	A1	19831101	CA 1980-357096	19800725
PRIORITY APPLN. INFO.:			DE 1979-2930542 A	19790727
			EP 1980-104267 A	19800719

ED Entered STN: 12 May 1984
AB Insulin was bound to polyethylene glycol monoalkyl ethers via the α-NH2 group of B-chain to give a product that formed aqueous dispersions for parenteral administration and gave >100% effect on blood glucose level with only 65% effect in the fat cell test. Thus, poly(ethylene glycol) monomethyl ether of mol. weight 1500 was treated with OCN(CH2)6NCO and bovine NαA1,NεB29-bis(tert-butoxycarbonyl)insulin and the deblocked to give insulin bound to the poly(ethylene glycol) monomethyl ether via a carbonylaminohexamethyleneaminocarbonyl group.
IC C07C103-52; C07C102-00; A61K037-26
CC 34-3 (Synthesis of Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 63
IT **78337-40-3P 78337-41-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

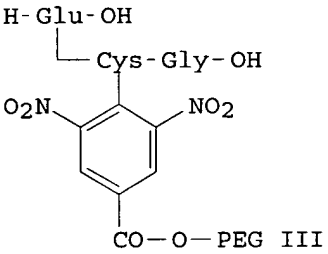
L10 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1979:457478 HCAPLUS
DOCUMENT NUMBER: 91:57478
TITLE: 4-Phenoxy-3,5-dinitrobenzoylpolyethyleneglycol: reversible attachment of cysteine-containing polypeptides to polymers in aqueous solutions
AUTHOR(S): Glass, John D.; Silver, Lester; Sondheimer, James; Pande, Chandra S.; Coderre, Jeffrey
CORPORATE SOURCE: Dep. Physiol. Biophys., Mt. Sinai Sch. Med., New York, NY, USA
SOURCE: Biopolymers (1979), 18(2), 383-92
CODEN: BIPMAA; ISSN: 0006-3525
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 May 1984
GI



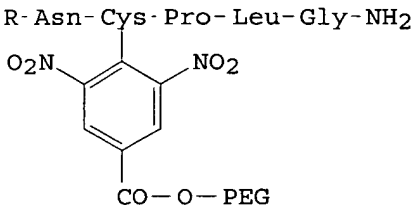
I



II



III



IV, R=Z-Arg

V, R=H

AB Polyethyleneglycol (PEG) (mol. weight 6000) was esterified with 4-phenoxy-3,5-dinitrobenzoyl chloride to give ester I, which reacted rapidly with SH groups of cysteine peptides in aqueous buffers (pH 7) to give a peptide-polymer thio compound linked by a dinitrophenylene bridge. I reacted very slowly with other functional groups of peptides; consequently, I can be selective for SH groups. Reduced glutathione and cystine peptide II (Z = PhCH2O2C) were treated with I to give peptide-polymer thio compds. III and IV, resp. IV underwent trypsin cleavage to give V; consequently, the PEG support does not restrict access of enzymes to peptide bonds. Bovine insulin B chain was also treated with I to give the appropriate peptide-polymer thio-linked compound

CC 34-3 (Synthesis of Amino Acids, Peptides, and Proteins)

IT 70687-74-0P 70687-76-2P **70815-57-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

=>

ANdre Kosar 10/075,097

```
=> d his

     (FILE 'REGISTRY' ENTERED AT 14:12:34 ON 10 MAR 2005)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 14:13:36 ON 10 MAR 2005
L1             1 S 25322-68-3
L2         99073 S C2H4O
               E INSULIN/CN
L3             1 S E3
L4          5862 S INSULIN AND PS/FS

     FILE 'HCAPLUS' ENTERED AT 14:15:21 ON 10 MAR 2005
L5         46709 S L2/D
L6          2168 S L3/D OR L4/D
L7         46709 S L1/D OR L5
L8            75 S L7 AND L6
L9        171687 S CONJUGATE?
L10           60 S L8 AND L9
L11        95240 S OLIGOMER?
L12            7 S L10 AND L11
L13      1248575 S  CHOLESTEROL OR ADAMANTANE OR FATTY ACID OR ALC?
L14           17 S L10 AND L13
L15           29 S INSULIN# (L) OLIGOMER (L) CONJUGATE#
L16            7 S L15 AND L13
L17           22 S L14 OR L16
```

```
=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 14:23:22 ON 10 MAR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 10 Mar 2005  VOL 142 ISS 11
FILE LAST UPDATED: 9 Mar 2005  (20050309/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d que l17
L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  25322-68-3
L2        99073 SEA FILE=REGISTRY ABB=ON  PLU=ON  C2H4O
L3            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN/CN
L4         5862 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN AND PS/FS
L5        46709 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2/D
L6         2168 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3/D OR L4/D
L7        46709 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1/D OR L5
L8           75 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND L6
L9       171687 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CONJUGATE?
L10          60 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND L9
L13     1248575 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CHOLESTEROL OR ADAMANTANE OR
                 FATTY ACID OR ALC?
L14          17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND L13
L15          29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  INSULIN# (L) OLIGOMER (L)
                 CONJUGATE#
L16           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND L13
L17          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 OR L16


=> d .ca l17 1-22
THE ESTIMATED COST FOR THIS REQUEST IS 65.34 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

L17  ANSWER 1 OF 22  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:34789  HCAPLUS
DOCUMENT NUMBER:          142:115130
TITLE:                    Production of emulsion-based microparticles containing
                          biological or chemical agents
INVENTOR(S):              Zeigerson, Ehud
PATENT ASSIGNEE(S):       PR Pharmaceuticals, USA
SOURCE:                   PCT Int. Appl., 30 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
```

C2H4O

=> D = derivatives

=> D = derivatives of insulin

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005003180	A2	20050113	WO 2004-US11485	20040412

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-461860P P 20030410
ED Entered STN: 14 Jan 2005
AB A method of preparing microparticles comprises (a) preparing a first phase comprising a solvent, an active agent, and a polymer, (b) preparing a second phase comprising a solvent, (c) passing the first phase and the second phase through a packed bed apparatus under laminar flow conditions to form microparticles, and (d) collecting the microparticles containing the active agent. The method provides emulsion-based microparticles having a narrow reproducible particle size distribution and containing biol. or chemical agents,
the method being used for both large and small scale production Thus, PEGylated insulin microspheres (mean diameter of 61 μm, D10 of 42 μm, D50 of 60 μm, D90 of 79 μm) were produced by obtaining a first phase comprising PEGylated insulin (213 mg) and glycolic acid-lactic acid copolymer (748 mg) in methylene chloride (10 mL), obtaining a second phase comprising polyvinyl **alc.** (2 g) in water (198 g), pumping the first phase through a packed bed apparatus (6 mm PTFE tubing, 150 mm long, filled with 500 μ glass beads) at a rate of 1.7 mL/min, pumping the second phase at a flow rate of 0.7 mL/min, collecting the emulsion, removing the solvent by evaporation, filtering the microspheres, washing with water, and drying.
IC ICM C08F
CC 37-6 (Plastics Manufacture and Processing)
Section cross-reference(s): 63
IT 50-50-0, Estradiol benzoate 362-07-2, 2-Methoxyestradiol **9004-10-8D**, Insulin, PEG **conjugates 25322-68-3D**, Poly(ethylene glycol), insulin **conjugates**
RL: MSC (Miscellaneous)
(microencapsulated; production of emulsion-based microparticles containing biol. or chemical agents)
IT 67-66-3, Chloroform, uses 75-09-2, Methylene chloride, uses 78-93-3, Methyl ethyl ketone, uses 100-51-6, Benzyl **alcohol**, uses 105-58-8, Diethyl carbonate 141-78-6, Ethyl acetate, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; production of emulsion-based microparticles containing biol. or chemical agents)

L17 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:817746 HCAPLUS
DOCUMENT NUMBER: 141:337642
TITLE: Biologically active material **conjugated** with biocompatible polymer with 1:1 complex, preparation

method thereof and pharmaceutical composition comprising the same

INVENTOR(S): Park, Myung-Ok
PATENT ASSIGNEE(S): Biopolymed Inc., S. Korea
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004084948	A1	20041007	WO 2004-KR701	20040327

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
KR 2003-19734	A	20030328
KR 2004-7983	A	20040206

ED Entered STN: 07 Oct 2004

AB The present invention relates to **conjugates** of biocompatible polymers and biol. active mols. wherein the activated biocompatible polymer is **conjugated** to a carboxyl group of biol. active material at a molar ratio of 1:1 and methods of preparation thereof and a pharmaceutical composition comprising the same. Preparation of mPEG(12000)-Hz-G-CDF **conjugate** is described and its biol. activity was determined

IC ICM A61K047-48
CC 63-5 (Pharmaceuticals)
ST biomaterial **conjugate** biocompatible polymer complex prepn
IT Agglutinins and Lectins
Antibodies and Immunoglobulins
Cytokines
Enkephalins
Growth hormone-releasing hormone receptors
Hemoglobins
Interleukins
Platelet-derived growth factors
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polyphosphazenes
Polysaccharides, biological studies
Polyurethanes, biological studies
Ricins
Transforming growth factors
Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates**; biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)
IT Polyamides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(poly(amino acids), **conjugates**; biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

IT Hypothalamic hormones
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(releasing factor, **conjugates**; biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α, **conjugates**; biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β, **conjugates**; biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ, **conjugates**; biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

IT **9004-74-4DP**, MPEG, hydrazide derivs., **conjugates** with biol. active mols.
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

IT 9000-96-8D, Arginase, **conjugates** 9001-05-2D, Catalase, **conjugates** 9001-25-6D, Blood coagulation factor VII, **conjugates** 9001-27-8D, Blood coagulation factor VIII, **conjugates** 9001-28-9D, Blood coagulation factor IX, **conjugates** 9001-34-7D, Galactosidase, **conjugates** 9001-37-0D, Glucose oxidase, **conjugates** 9001-45-0D, Glucuronidase, **conjugates** 9001-62-1D, Lipase, **conjugates** 9002-10-2D, Tyrosinase, **conjugates** 9002-12-4D, Uricase, **conjugates** 9002-64-6D, Parathyroid hormone, **conjugates** 9002-71-5D, Thyroid stimulating hormone, **conjugates** **9002-89-5D**, Polyvinyl **alcohol**, **conjugates** 9003-01-4D, Polyacrylic acid, **conjugates** 9003-05-8D, Polyacryl amide, **conjugates** 9003-39-8D, Polyvinyl pyrrolidone, **conjugates** 9004-07-3D, Chymotrypsin, **conjugates** **9004-10-8D**, Insulin, **conjugates** 9004-54-0D, Dextran, **conjugates** 9007-12-9D, Calcitonin, **conjugates** 9015-68-3D, Asparaginase, **conjugates** 9026-93-1D, Adenosine deaminase, **conjugates** 9027-69-4D, Adenosine diphosphatase, **conjugates** 9027-98-9D, Arginine deiminase, **conjugates** 9033-06-1D, Glucosidase, **conjugates** 9034-40-6D, Luteinizing hormone-releasing hormone, **conjugates** with biocompatible polymer 9054-89-1D, Superoxide dismutase, **conjugates** 11096-26-7D, Erythropoietin, **conjugates** 25104-18-1D, Poly(L-lysine), **conjugates** **25322-68-3D**, Polyethylene glycol, **conjugates** 25322-69-4D, Polypropyleneglycol, **conjugates** 26023-30-3D, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], **conjugates** 26100-51-6D, Polylactic acid, **conjugates** 38000-06-5D, Poly(L-lysine), **conjugates** 62229-50-9D, Epidermal growth factor, **conjugates** 63340-72-7D, Thymic humoral factor,

conjugates 83652-28-2D, Calcitonin gene related peptide, **conjugates** 83869-56-1D, Granulocyte macrophage colony stimulatingfactor, **conjugates** 143011-72-7D, Granulocytecolony stimulating factor, **conjugates** 345260-48-2D, Polytrimethylene glycol, **conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biol. active material **conjugated** with biocompatible polymer with 1:1 complex, preparation method thereof and pharmaceutical composition comprising same)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:609742 HCAPLUS
DOCUMENT NUMBER: 141:162351
TITLE: Peptides capable of facilitating penetration across a biological barrier and their use in drug delivery
INVENTOR(S): Ben-Sasson, Shmuel A.; Cohen, Einat
PATENT ASSIGNEE(S): Israel
SOURCE: U.S. Pat. Appl. Publ., 54 pp., Cont.-in-part of Appl. No. PCT/03IB/00968.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004146549	A1	20040729	US 2003-665184	20030917
WO 2003066859	A2	20030814	WO 2003-IB968	20030207
WO 2003066859	A3	20040513		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-355396P P 20020207
WO 2003-IB968 A2 20030207

ED Entered STN: 30 Jul 2004
AB The invention relates to amino acid sequences capable of facilitating penetration of an effector across a biol. barrier such as epithelial and endothelial cell layers. The invention also relates to methods of treating or preventing diseases by administering penetrating modules to affected subjects. Thus, a conserved peptide sequence from an Haemophilus influenzae protein involved in paracytosis facilitates penetration of this bacterium between human lung epithelial cells without compromising the epithelial barrier. This peptide, and similar peptides from other bacteria or from human NK-1 and NK-2 receptors, are disclosed. One such peptide, derived from E. coli YCFC protein, when fused to insulin, facilitated its passage across the mouse intestine and caused lowering of blood glucose levels.
IC ICM A61K038-00
ICS A61K009-70; A61K031-715
NCL 424449000; 514002000; 514054000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 34

IT Diglycerides
Fatty acids, biological studies
Glycerides, biological studies
Monoglycerides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aliphatic hydrophobic mol., peptide comprising; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT Antibiotics
Anticoagulants
Antitumor agents
Drugs
Immunomodulators
(**conjugates** with peptides; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates** with peptides; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT **Fatty acids**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(long-chain, peptide acylation utilizes; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT Detergents
(peptide **conjugate**; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT Enkephalins
Glycosaminoglycans, biological studies
Polysaccharides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide **conjugates**; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT **Alcohols**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(polyhydric, water soluble solvent, peptide comprising; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT 516-50-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide-therapeutic substance **conjugates** and; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT 616-91-1, N-Acetyl-L-cysteine 9078-38-0, Soybean trypsin inhibitor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide-therapeutic substance **conjugates**; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT 516-50-7D, peptide **conjugate 25322-68-3D**, Polyethylene glycol, peptide **conjugates 691397-13-4D**, Pluronic F-68, peptide **conjugate**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT 68-19-9D, Vitamin B12, **conjugates** with peptides 1403-66-3D, Gentamycin, fusion product 1404-04-2D, Neomycin, fusion product 8001-27-2D, Hirudin, analogs, fusion products 8001-27-2D, Hirudin, fusion product 9002-64-6, Parathyroid hormone 9002-67-9, Luteinizing

hormone 9002-68-0, Follicle-stimulating hormone 9002-72-6D, Somatotropin, fusion products 9002-79-3D, MSH, fusion products **9004-10-8D**, Insulin, fusion products 9004-61-9D, Hyaluronic acid, fusion products 9005-49-6D, Heparin sulfate, fusion products 9007-12-9, Calcitonin 9007-28-7D, Chondroitin sulfate, fusion products 9034-40-6D, Luteinizing hormone releasing hormone, analogs, fusion products 9041-92-3, α1-Antitrypsin 11096-26-7D, Erythropoietin, fusion products 24967-94-0D, Dermatan sulfate, fusion products 32986-56-4D, Tobramycin, fusion product 37213-49-3D, α-Melanocyte-stimulating hormone, fusion products 37517-28-5D, Amikacin, fusion product 70904-56-2D, Kyotorphin, fusion product 70904-56-2D, Kyotorphin, fusion products 81733-79-1D, Dalargin, fusion product 81733-79-1D, Dalargin, fusion products 83869-56-1D, GM-CSF, fusion products 89750-14-1D, Glucagon-like peptide 1, fusion products 106096-93-9D, Basic fibroblast growth factor, fusion products 128270-60-0D, Hirulog, fusion product 162808-62-0D, Caspofungin, fusion products
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

IT 53-79-2, Puromycin 55-91-4, DFP 56-45-1D, L-Serine, borate complexes 60-00-4, EDTA, biological studies 66-71-7, 1,10-Phenanthroline 92-52-4D, Biphenyl, boronic acid derivs. and sugar complexes 329-98-6, PMSF 501-52-0, Benzenepropanoic acid 863-57-0, Sodium-glycocholate 1405-87-4, Bacitracin 2364-87-6, TLCK 3858-83-1, p-Aminobenzamidine 6303-21-5D, Phosphinic acid, dipeptide analogs 9003-01-4D, 2-Propenoic acid homopolymer, derivs. 9012-76-4D, Chitosan, EDTA **conjugates** 9076-44-2, Chymostatin 9087-70-1, Aprotinin 10043-35-3D, Boric acid, L-serine complexes 13780-71-7D, Boronic acid, biphenyl derivs. and sugar complexes 13780-71-7D, Boronic acid, α-amino derivs. 30827-99-7, AEBSF 36357-77-4, Phosphoramidon 37205-61-1, Protease inhibitor 37330-34-0, BowmanBirk inhibitor 37691-11-5, Antipain 42228-92-2, Acivicin 51798-45-9, Elastatinal 55123-66-5, Leupeptin 58970-76-6, Bestatin 59721-28-7 67655-94-1, Amastatin 71933-13-6, APMSF 76721-89-6, Thiorphan 88105-67-3 89703-10-6, FK-448
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(protective agent, peptide comprising; peptides capable of facilitating penetration across biol. barrier and their use in drug delivery)

L17 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:162445 HCAPLUS
DOCUMENT NUMBER: 140:193075
TITLE: Pharmaceutical compositions of **insulin** drug-**oligomer conjugates** and methods of treating diseases therewith
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingam; Ekwuribe, Nnochiri N.; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 235,284.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004038866	A1	20040226	US 2003-382155	20030305

US 2003069170	A1	20030410	US 2002-235284	20020905
US 6770625	B2	20040803		
PRIORITY APPLN. INFO.:			US 2001-318193P	P 20010907
			US 2002-377865P	P 20020503
			US 2002-235281	A2 20020905
			US 2002-235284	A2 20020905

OTHER SOURCE(S): MARPAT 140:193075
ED Entered STN: 29 Feb 2004
AB Pharmaceutical compns. that include **insulin**, an **insulin** drug-**oligomer conjugate**, a **fatty acid** component, and a bile salt component or a bile salt component without a **fatty acid** component are described. The **insulin** drug is covalently coupled to an oligomeric moiety. The **fatty acid** component and the bile salt component, when together, can be present in a weight-to-weight ratio of between 1:15 and 15:1. Methods of treating an **insulin** deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. Substantial redns. in blood glucose were observed as the result of coadministration of hexyl-**insulin** monoconjugate 2 (HIM2) and bile salts to mice and dogs. All of the bile salts were effective at a level of 1.5 %.
IC ICM A61K038-28
ICS A61K031-57
NCL 514003000; 514171000
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
ST pharmaceutical **insulin** drug **oligomer conjugate** antidiabetic; blood glucose redn **insulin conjugate** bile salt
IT **Fatty acids**, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C4-20; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems
(buccal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Alkanes, biological studies
Oligomers
Polyoxyalkylenes, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates** with **insulin**; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Digestive tract
(**insulin oligomer conjugate** delivery across wall of; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems
(liqs., oral; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems
(liqs.; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems
(nasal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Antidiabetic agents
Drug delivery systems

(oral; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(parenterals; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Antidiabetic agents
Buffers
Drug delivery systems
Human
Hydrophilicity
Lipophilicity
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Bile salts
Fatty acids, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Polyoxyalkylenes, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(solids; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Flavoring materials
(strawberry; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(tablets; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(transdermal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 9004-10-8, **Insulin**, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deficiency or disorder, treatment of; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 81-24-3 81-25-4 83-44-3 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 145-42-6, Sodium taurocholate 334-48-5, Capric acid 360-65-6 361-09-1, Sodium Cholate 516-50-7 863-57-0 1180-95-6, Sodium taurodeoxycholate 2898-95-5, Sodium ursodeoxycholate **9004-10-8D**, **Insulin**, **conjugates** with **oligomers 11061-68-0D**, **Insulin** (human), **conjugates** with methoxy(polyethylene glycol) hexanoic acid **11061-68-0D**, **Insulin** (human), **conjugates** with polypropylenglycols **25322-68-3D**, Polyethylene glycol, **conjugates** with **insulin** **116094-23-6D**, AspB28insulin, human, **conjugates** with **oligomers 133107-64-9D**, **conjugates** with **oligomers 326892-09-5D**, **conjugates** with human **insulin 452310-88-2D**, **conjugates** with

oligomers 452310-92-8D, **conjugates** with
oligomers 452311-02-3D, **conjugates** with
oligomers 452311-09-0D, **conjugates** with
oligomers 452311-17-0D, **conjugates** with
oligomers 452311-24-9D, **conjugates** with
oligomers 452311-26-1D, **conjugates** with
oligomers 452311-27-2D, **conjugates** with
oligomers 452311-29-4D, **conjugates** with
oligomers 452311-30-7D, **conjugates** with
oligomers 452311-31-8D, **conjugates** with
oligomers 452311-32-9D, **conjugates** with
oligomers 452311-33-0D, **conjugates** with
oligomers 452311-35-2D, **conjugates** with
oligomers 452311-36-3D, **conjugates** with
oligomers 452311-37-4D, **conjugates** with
oligomers 502487-21-0D, **conjugates** with human
insulin 502495-36-5D, **conjugates** with
oligomers 663602-55-9D, **conjugates** with human
insulin 663602-56-0D, **conjugates** with human
insulin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 100-44-7, Benzyl chloride, reactions 111-77-3, Diethylene glycol monomethyl ether 112-27-6, Triethylene glycol 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 124-63-0, Methanesulfonyl chloride 141-78-6, EtOAc, reactions 623-65-4, Palmitic anhydride 865-47-4 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8, Hexaethylene glycol 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6, 8-Bromooctanoic acid 25322-68-3, PEG6 25952-53-8, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 3639-35-8P 4437-01-8P, Heptaethylene glycol monomethyl ether 10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether 29823-21-0P 70802-40-3P 74654-05-0P 86259-87-2P, Tetraethylene glycol monobenzyl ether 105292-71-5P 124668-93-5P 142556-85-2P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-67-0P 477775-68-1P 477775-69-2P 477775-73-8P 477775-74-9P 477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-23-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 27425-92-9P, Decaethylene glycol monomethyl ether 62304-85-2P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477788-13-9P 502487-22-1P 502487-24-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

IT 69-65-8, Mannitol 77-86-1, Tromethamine 77-92-9, Citric Acid, biological studies 102-71-6, Trolamine, biological studies 557-04-0, Magnesium Stearate 994-36-5, Sodium Citrate 1310-73-2, Sodium Hydroxide, biological studies 7558-79-4, Dibasic Sodium Phosphate 7558-80-7, Sodium Phosphate Monobasic 7647-01-0, Hydrochloric Acid, biological studies 7732-18-5, Water, biological studies 9004-34-6, Cellulose, biological studies 9063-38-1, Explotab 56038-13-2,

Sucralose 74811-65-7, Croscarmellose Sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer** **conjugates** for treating diseases)

L17 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:142842 HCAPLUS
DOCUMENT NUMBER: 140:193028
TITLE: Peptide-conjugated oligomeric compounds for enhanced cellular uptake of the oligomers
INVENTOR(S): Manoharan, Muthiah; Maier, Martin
PATENT ASSIGNEE(S): ISIS Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 41 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004034191	A1	20040219	US 2002-222595	20020816
WO 2004016274	A2	20040226	WO 2003-US25567	20030815
WO 2004016274	A3	20040325		
WO 2004016274	B1	20040527		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-222595 A2 20020816
OTHER SOURCE(S): MARPAT 140:193028
ED Entered STN: 22 Feb 2004
AB The invention discloses amphipathic peptide-conjugated oligomeric compds. (e.g. peptide conjugates with oligonucleotides or with peptide nucleic acids), as well as methods of making and using such compds. The invention further discloses methods for enhancing the cellular uptake of oligomeric compds. comprising conjugating the compds. to amphipathic moieties, e.g. amphipathic peptides. Methods for synthesizing the conjugates are included.
IC ICM A61K048-00
ICS C07K009-00; A61K038-14
NCL 530322000; 514008000
CC 1-2 (Pharmacology)
Section cross-reference(s): 33, 34
IT 57-88-5, **Cholesterol**, biological studies 59-23-4, Galactose, biological studies 59-30-3, biological studies 63-42-3, Lactose 68-19-9, Vitamin B12 3458-28-4, Mannose 7535-00-4, Galactosamine 9004-10-8, **Insulin**, biological studies 9061-61-4, Nerve growth factor 15687-27-1, Ibuprofen 62229-50-9, Epidermal growth factor 99896-85-2, Arginylglycylaspartic acid
RL: BSU (Biological study, unclassified); BIOL (Biological study) (targeting moiety; peptide-**conjugated** oligomeric compds. for enhanced cellular uptake of **oligomers**)

L17 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:570791 HCAPLUS
DOCUMENT NUMBER: 139:122771
TITLE: Use of oligomers and polymers for drug solubilization, stabilization, and delivery
INVENTOR(S): Soane, David S.; Suich, Daniel J.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059321	A1	20030724	WO 2002-US41416	20021223
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003180244	A1	20030925	US 2002-328898	20021223
EP 1465598	A1	20041013	EP 2002-794421	20021223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PRIORITY APPLN. INFO.:			US 2001-343483P	P 20011221
			WO 2002-US41416	W 20021223

ED Entered STN: 25 Jul 2003
AB The use of **oligomers** and polymers capable of rendering insol. drugs soluble, protecting unstable drugs, and facilitating the delivery of drugs to their site of action is described. A "smart" surfactant is provided comprising a hydrophobic element, e.g., a small mol. or an **oligomer** or polymer, covalently attached to a hydrophilic element, capable of forming a micelle that encapsulates a hydrophobic drug. This invention further relates to processes for the preparation of such **oligomers** and polymers, and to compns. containing them. For example, oral delivery of **insulin** by transcytosis was presented. **Insulin** is **conjugated** to a polar loading element of a smart surfactant for the formation of polar-core micelles with the **insulin** contained in the core. The hydrophobic element of the smart surfactant is comprised of a hydrophobic peptoid **oligomer**, and the hydrophilic element contains an ester linkage which is a substrate for intestinal lipase. The micelles protect the **insulin** from the degradative enzymes and gastric pH. The micelles travel to the small intestine, where lipases cleave the ester linkage in the hydrophilic element. The cleavage of this linker unmasks the monosaccharide ligand, which then binds to lectins present on the apical membrane surface of mucosal enterocyte, localizing the micelles to the cells. The micelles then cross the mucosal enterocytes by receptor-mediated transcytosis induced by the binding of the ligand to the lectin, which transports the micelles to the bloodstream. Gradual decomposition of the micelles, initiated by cleavage of the hydrophilic element, results in the release of **insulin** into the bloodstream.
IC ICM A61K009-127

ICS A61K009-14; A61K009-50; A61K009-20; A61F013-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2, 33, 34
IT 50-99-7, D-Glucose, biological studies 57-88-5, **Cholesterol**, biological studies 9004-53-9, Dextrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligomers and polymers for drug solubilization, stabilization, and delivery by micellization)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:221462 HCAPLUS
DOCUMENT NUMBER: 138:260437
TITLE: Pharmaceutical compositions of drug-oligomer **conjugates** for oral administration
INVENTOR(S): Soltero, Richard; Ekwuribe, Nnochiri N.; Opawale, Foyeke; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003022210	A2	20030320	WO 2002-US28536		20020906
WO 2003022210	A3	20031218			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003083232	A1	20030501	US 2002-235381		20020905
PRIORITY APPLN. INFO.:			US 2001-318193P	P	20010907
			US 2002-377865P	P	20020503

ED Entered STN: 21 Mar 2003
AB An oral pharmaceutical composition comprising a drug-**oligomer conjugate**, 0.1-15% of a **fatty acid** component, and 0.1-15% of a bile salt component is described. The drug, e.g., a peptide or protein, is covalently coupled to an oligomeric moiety. The **fatty acid** component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating diseases in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. For example, tablets containing an **insulin conjugate** HIM2 were prepared by lyophilization of a mixture containing HIM2 2.5 g, Na cholate 30.0 g, oleic acid 10.0 g, 25% sucralose 8.0 g, flavor 4.0 g, capric acid 5.0 g, lauric acid 5.0 g, citric acid 67.2 g, trolamine 42.4 g, NaOH 18.8 g, pH adjusters (5N NaOH and 5N HCl) as needed, and water resulting in an amorphous powder. The powder (127.6 g)

was blended with citric acid 29.7 g, sodium citrate 84.2 g, Tris base 106.7 g, microcryst. cellulose 24.8 g, and Explotab 9.4 g and compressed into tablets.

IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 35
ST oral drug oligomer **conjugate** bile salt **fatty acid**; peptide protein drug oligomer **conjugate** oral
IT Drug delivery systems
(liqs., oral; oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT **Fatty acids**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-chain; oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT **Fatty acids**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medium-chain; oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT Antidiabetic agents
Buffers
Human
(oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT Bile salts
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT Drug delivery systems
(oral; oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT Drug delivery systems
(tablets; oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT **11061-68-0D**, Human **insulin**, **conjugates** with methoxy(polyethylene glycol) hexanoic acid **326892-09-5D**, **conjugates** with human **insulin**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-**oligomer conjugates** containing bile salt and **fatty acid**)
IT 9007-12-9D, Calcitonin, oligomer **conjugates** 59112-80-0D, C-Peptide, oligomer **conjugates**
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT 77-86-1, Tromethamine 102-71-6, Trolamine, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate 47931-85-1D, Salmon calcitonin, oligomer **conjugates** 477775-65-8D, drug **conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-oligomer **conjugates** containing bile salt and **fatty acid**)
IT 100-44-7, Benzyl chloride, reactions 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8, Hexaethylene glycol 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6,

8-Bromooctanoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of oligomers for drug-oligomer **conjugates** for oral delivery)

IT 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol
10108-28-8P 24342-68-5P 27425-92-9P 29823-21-0P 60037-74-3P
74654-05-0P 86259-87-2P 113395-48-5P 124668-93-5P 477775-57-8P
477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P
477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P
477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P
477788-13-9P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P
502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of oligomers for drug-oligomer **conjugates** for oral delivery)

L17 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:221460 HCAPLUS
DOCUMENT NUMBER: 138:260435
TITLE: Pharmaceutical compositions of **insulin** drug-**oligomer conjugates**
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingham; Ekwuribe, Nnochiri N.; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003022208	A2	20030320	WO 2002-US28429		20020906
WO 2003022208	A3	20030925			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003083232	A1	20030501	US 2002-235381		20020905
PRIORITY APPLN. INFO.:			US 2001-318193P	P	20010907
			US 2002-377865P	P	20020503

OTHER SOURCE(S): MARPAT 138:260435
ED Entered STN: 21 Mar 2003
AB Pharmaceutical compns. that include an **insulin** drug-**oligomer conjugate**, a **fatty acid** component, and a bile salt component are described. The **insulin** drug is covalently coupled to an oligomeric moiety. The **fatty acid** component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating an **insulin** deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing

such pharmaceutical compns. E.g., PEG derivs. of **fatty acids** such as hexanoic acid were prepared, activated and **conjugated** to **insulin** derivs.

IC ICM A61K

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 34, 35

ST insulin PEG **fatty acid** conjugate pharmaceutical

IT Drug delivery systems
(oral; pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT Drug delivery systems
(solids; pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 361-09-1, Sodium cholate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 111-77-3 112-35-6 112-60-7 112-76-5, Stearoyl chloride 623-65-4, Palmitic anhydride 2615-15-8 15848-88-1 23601-40-3, 2,5,8,11,14,17-Hexaoxanonadecan-19-ol 142556-85-2 477788-13-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 3639-35-8P, Decanoic acid, 10-hydroxy-, ethyl ester 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 5299-60-5P, Ethyl 6-hydroxyhexanoate 10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 29823-21-0P, Ethyl 8-bromooctanoate 60037-74-3P 74654-05-0P 86259-87-2P 105292-71-5P 113395-48-5P 124668-93-5P 259228-98-3P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P 477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P 502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 9004-10-8DP, **Insulin**, **conjugates** with **fatty acid**-PEG derivs.
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 502495-05-8 502495-19-4 502495-22-9 502495-24-1 502495-25-2 502495-35-4 502495-36-5 502495-38-7 502495-39-8 502495-40-1 502495-41-2 502495-42-3 502495-43-4 502495-44-5 502495-47-8 502495-48-9 502495-51-4 502495-52-5 502495-53-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

L17 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:657913 HCAPLUS
DOCUMENT NUMBER: 137:196046
TITLE: Methods of treating diabetes mellitus with orally administered insulin oligomers
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Still, James Gordon; Filbey, Jennifer Ann

PATENT ASSIGNEE(S): Nobex Corporation, USA; Radhakrishnan, Balasingam; Ansari, Aslam M.; Odenbaugh, Amy L.
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002065985	A2	20020829	WO 2002-US4440		20020214
WO 2002065985	A3	20040219			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2003050228	A1	20030313	US 2002-75097		20020213
CA 2437940	AA	20020829	CA 2002-2437940		20020214
EP 1409006	A2	20040421	EP 2002-709541		20020214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004527487	T2	20040909	JP 2002-565546		20020214
PRIORITY APPLN. INFO.:			US 2001-269198P	P	20010215
			US 2002-347713P	P	20020111
			WO 2002-US4440	W	20020214

ED Entered STN: 30 Aug 2002

AB Methods of treating diabetes mellitus using an effective amount of an oral insulin derivative are claimed. The structure of the insulin derivative is: insulin polypeptide-B-Lj-Gk-R-G'm-R'-G"n-T wherein: B is a bonding moiety; L is a linker moiety; G, G' and G" are individually selected spacer moieties; R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety; T is a terminating moiety; and j, k, m and n are individually 0 or 1. The structure of the insulin derivative is: insulin polypeptide-X(CH2)mY(C2H4O)nR, insulin polypeptide-X(CH2)m(OC2H4)nOR, or insulin polypeptide-NH-CO-(CH2)m(OC2H4)nOR, wherein: X and Y are ester moieties, thioester moieties, ether moieties, carbamate moieties, thiocarbamate moieties, carbonate moieties, thiocarbonate moieties, amide moieties, urea moieties or covalent bonds; m is between 1 and 24; n is between 1 and 50; and R is an alkyl moiety, a sugar moiety, **cholesterol**, **adamantane**, an **alc.** moiety, or a **fatty acid** moiety. A specifically claimed derivative is insulin polypeptide-NH-CO-(CH2)5(OC2H4)7OCH3. Formulations for capsules are exemplified.

IC ICM A61K
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 63
ST diabetes mellitus treatment oral **insulin oligomer conjugate**
IT 9004-10-8D, **Insulin**, oligomeric **conjugates** 452310-88-2D, oligomeric **conjugates** 452310-92-8D, oligomeric **conjugates** 452311-02-3D, oligomeric **conjugates** 452311-09-0D, oligomeric **conjugates** 452311-17-0D, oligomeric **conjugates** 452311-24-9D, oligomeric **conjugates**

452311-25-0D, oligomeric **conjugates** 452311-26-1D, oligomeric **conjugates** 452311-27-2D, oligomeric **conjugates** 452311-28-3D, oligomeric **conjugates** 452311-29-4D, oligomeric **conjugates** 452311-30-7D, oligomeric **conjugates** 452311-31-8D, oligomeric **conjugates** 452311-32-9D, oligomeric **conjugates** 452311-33-0D, oligomeric **conjugates** 452311-34-1D, oligomeric **conjugates** 452311-35-2D, oligomeric **conjugates** 452311-36-3D, oligomeric **conjugates** 452311-37-4D, oligomeric **conjugates** 452311-38-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treating diabetes mellitus with orally administered **insulin oligomers**)

L17 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:107165 HCAPLUS
DOCUMENT NUMBER: 136:172754
TITLE: Highly reactive branched polymer and proteins or peptides **conjugated** with the polymer
INVENTOR(S): Park, Myung-Ok; Lee, Kang-Choon; Cho, Sung-hHe
PATENT ASSIGNEE(S): S. Korea
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009766	A1	20020207	WO 2001-KR1209	20010713
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
KR 2002010363	A	20020204	KR 2000-44046	20000729

PRIORITY APPLN. INFO.: KR 2000-44046 A 20000729
ED Entered STN: 10 Feb 2002
AB The present invention relates to new biocompatible polymer derivs., and a protein-polymer or a peptide-polymer which is produced by conjugation of biol. active protein and peptide with the biocompatible polymer derivs. More particularly, the present invention relates to a highly reactive branched biocompatible polymer derivative containing a long linker between polymer derivs. and protein or peptide mols., which is minimized in decrease the biol. activity of proteins by conjugating the less number of polymer derivs. to the active sites of proteins, improved in water solubility, and protected from being degraded by protease. In hence, the highly reactive branched biocompatible polymer-proteins or peptides **conjugates** with long linker retain the biol. activity for a long period of time and improve a bioavailability of bioactive proteins and peptides. For example, activated PEG-interferon **conjugates** were prepared by adding 3 mg of succinic N-hydroxysuccinimidyl di-PEG to 3 mg of interferon in 0.1 M phosphate buffer solution, pH 7.0 at ambient temperature The reaction was stopped

with 0.1 M glycine and the excess reagents were using Centricon-30.
IC ICM A61K047-48
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 7, 15, 37
ST biocompatible peptide polymer **conjugate** bioavailability; protein polymer **conjugate** biocompatible bioavailability
IT Polyoxyalkylenes, biological studies
Polyphosphazenes
Polysaccharides, biological studies
Polyurethanes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with peptides or proteins; highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Polymers, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, with peptides or proteins; highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Proteins
RL: SPN (Synthetic preparation); PREP (Preparation)
(**conjugates**, with polymers; highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Peptides, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**, with polymers; highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Biocompatibility
(highly reactive branched biocompatible polymers and their **conjugates** with proteins or peptides)
IT Drug delivery systems
(highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Agglutinins and Lectins
Antibodies and Immunoglobulins
Cytokines
Enkephalins
Hemoglobins
Interleukins
Platelet-derived growth factors
Ricins
Transforming growth factors
Tumor necrosis factors
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polymer **conjugates**; highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Interferons
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(α, polymer **conjugates**; highly reactive branched polymers and their **conjugates** with proteins or peptides)
IT Interferons
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(β, polymer **conjugates**; highly reactive branched polymers and their **conjugates** with proteins or peptides)

IT Interferons
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(γ, polymer **conjugates**; highly reactive branched polymers and their **conjugates** with proteins or peptides)

IT 9004-74-4, Methoxy poly(ethylene glycol)
RL: RCT (Reactant); RACT (Reactant or reagent)
(highly reactive branched polymers and their **conjugates** with proteins or peptides)

IT 67665-18-3P 92451-01-9P 395645-04-2P 395645-05-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(highly reactive branched polymers and their **conjugates** with proteins or peptides)

IT 395645-06-4P 395645-07-5P 395645-08-6P 395645-09-7P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(highly reactive branched polymers and their **conjugates** with proteins or peptides)

IT 9000-96-8DP, Arginase, polymer **conjugates** 9001-05-2DP, Catalase, polymer **conjugates** 9001-25-6DP, Blood-coagulation factor VII, polymer **conjugates** 9001-28-9DP, Factor IX, polymer **conjugates** 9001-34-7DP, Galactosidase, polymer **conjugates** 9001-37-0DP, Glucose oxidase, polymer **conjugates** 9001-45-0DP, Glucuronidase, polymer **conjugates** 9001-62-1DP, Lipase, polymer **conjugates** 9002-10-2DP, Tyrosinase, polymer **conjugates** 9002-12-4DP, Uricase, polymer **conjugates** 9002-64-6DP, Parathyroid hormone, polymer **conjugates** 9002-71-5DP, Thyroid stimulating hormone, polymer **conjugates** 9002-72-6DP, Growth hormone, **conjugates** with PEG derivative 9002-72-6DP, Somatotropin, polymer **conjugates** **9002-89-5DP**, Polyvinyl **alcohol**, **conjugates** with peptides or proteins 9003-01-4DP, Polyacrylic acid, **conjugates** with peptides or proteins 9003-05-8DP, Polyacrylamide, **conjugates** with peptides or proteins 9004-07-3DP, Chymotrypsin, polymer **conjugates** **9004-10-8DP**, Insulin, polymer **conjugates** 9004-54-0DP, Dextran, **conjugates** with peptides or proteins 9007-12-9DP, Calcitonin, polymer **conjugates** 9015-68-3DP, Asparaginase, polymer **conjugates** 9026-93-1DP, Adenosine deaminase, polymer **conjugates** 9027-69-4DP, Adenosine diphosphatase, polymer **conjugates** 9027-98-9DP, polymer **conjugates** 9033-06-1DP, Glucosidase, polymer **conjugates** 9034-40-6DP, LHRH, polymer **conjugates** 9054-89-1DP, Superoxide dismutase, polymer **conjugates** 25104-18-1DP, Poly(L-lysine), **conjugates** with peptides or proteins **25322-68-3DP**, Polyethylene glycol, **conjugates** with peptides or proteins 25322-69-4DP, Polypropylene glycol, **conjugates** with peptides or proteins 26023-30-3DP, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], **conjugates** with peptides or proteins 26100-51-6DP, Polylactic acid, **conjugates** with peptides or proteins 31714-45-1DP, **conjugates** with peptides or proteins 38000-06-5DP, Poly(L-lysine), **conjugates** with peptides or proteins 62229-50-9DP, EGF, **conjugates** with PEG derivative 62229-50-9DP, Epidermal growth factor, polymer **conjugates** 63340-72-7DP, Thymic humoral factor, polymer **conjugates** 83652-28-2DP, Calcitonin gene related peptide, polymer **conjugates** 83869-56-1DP, Granulocyte-macrophage colony-stimulating factor, polymer **conjugates** 113189-02-9DP, Factor VIII, polymer

conjugates 143011-72-7DP, Granulocyte colony-stimulating factor, polymer **conjugates** **395645-02-0DP, conjugates** with peptides or proteins **395645-03-1DP, conjugates** with peptides or proteins
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(highly reactive branched polymers and their **conjugates** with proteins or peptides)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:851191 HCAPLUS
DOCUMENT NUMBER: 135:376868
TITLE: Derivatization of proteins for prolonged circulation and enhanced storage stability
INVENTOR(S): Gregoriadis, Gregory
PATENT ASSIGNEE(S): Lipoxen Technologies Limited, UK
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001087922	A2	20011122	WO 2001-GB2115		20010514
WO 2001087922	A3	20030530			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
EP 1335931	A2	20030820	EP 2001-931843		20010514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003533537	T2	20031111	JP 2001-585141		20010514
US 2003129159	A1	20030710	US 2002-276552		20021118
PRIORITY APPLN. INFO.:			EP 2000-304108	A	20000516
			WO 2001-GB2115	W	20010514

ED Entered STN: 23 Nov 2001
AB Proteins are derivatized by reaction of pendant groups, usually groups which are side chains in non-terminal amino acyl units of the protein, in aqueous reactions in the presence of a denaturant. The denaturant is preferably an amphiphilic compound, most preferably an anionic amphiphilic compound such as a long chain alkyl sulfate mono ester, preferably an alkaline metal salt, for instance sodium dodecyl sulfate. The degree of derivatization is increased, while the protein retains activity, such as enzyme activity. The increase in the degree of derivatization enhances the increase in circulation time in vivo and stability on storage in vitro. Preferably the derivatizing reagent is an aldehyde compound which reacts with primary amine groups, generally the epsilon-amino group of lysyl units. Derivatization is conducted under reducing conditions to generate a secondary amine derivative For example, IgG was subjected to

derivatization with polysialic acid (oxidized colominic acid) or monomethoxy poly(ethylene glycol) succinimidyl succinate in the absence and presence of 10-3M sodium dodecyl sulfate (SDS). The presence of SDS increased the level of derivatization for a PEG reagent as well as for a polysialic acid reagent. The PEG reagent gave a higher degree of substitution than the colominic acid reagent.

IC ICM C07K001-00
CC 63-8 (Pharmaceuticals)
Section cross-reference(s): 1, 2, 15, 34
IT Immunoglobulins
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(G, **conjugates**, with colominic acid or PEG; derivatization of proteins for prolonged circulation and enhanced storage stability)
IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with proteins; derivatization of proteins for prolonged circulation and enhanced storage stability)
IT Proteins, specific or class
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**; derivatization of proteins for prolonged circulation and enhanced storage stability)
IT Sialic acids
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polymers, **conjugates** with proteins; derivatization of proteins for prolonged circulation and enhanced storage stability)
IT 9001-05-2DP, Catalase, **conjugates** with colominic acid
9004-10-8DP, Insulin, **conjugates** with colominic acid, biological studies 9013-15-4DP, Colominic acid, **conjugates** with proteins 9087-70-1DP, Aprotinin, **conjugates** with colominic acid **25322-68-3DP**, Poly(ethylene glycol), **conjugates** with proteins
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(derivatization of proteins for prolonged circulation and enhanced storage stability)
IT 9002-89-5, Polyvinyl **alcohol** 25322-68-3, Polyethylene glycol 78274-32-5, Methoxypolyethylene glycol succinimidyl succinate
RL: RCT (Reactant); RACT (Reactant or reagent)
(derivatizing agent; derivatization of proteins for prolonged circulation and enhanced storage stability)

L17 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:590411 HCAPLUS
DOCUMENT NUMBER: 136:156308
TITLE: Biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alcohol**) for oral vaccine delivery
AUTHOR(S): Kissel, T.; Jung, T.; Kamm, W.; Breitenbach, A.
CORPORATE SOURCE: Department of Pharmaceutics and Biopharmacy, Philipps University, Marburg, Germany
SOURCE: Macromolecular Symposia (2001), 172(Polymers in Medicine), 113-125
CODEN: MSYMEC; ISSN: 1022-1360
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 15 Aug 2001
AB Small nanospheres prepared by spontaneous polymer - protein self-assembling are an attractive concept for the preparation of nanoscale drug delivery systems, since the use of solvents and surfactants can be avoided. For this purpose, polyesters were prepared by grafting poly(lactic acid-co-glycolic acid) (PLGA) chains onto poly(vinyl **alc.**) (PVAL) or the neg. charged sulfobutylated poly(vinyl **alc.**), P(SBVE). Adjustment of PLGA chain lengths by feed composition allowed to modify polymer properties, such as mol. weight and solubility While polyesters with a chain length of 5-10 lactic or glycolic acid units showed on average good solubility in acetone, further chain length reduction yielded water-soluble polymers. In aqueous solution, a lower critical solution temperature was observed Spontaneous formation of colloidal polymer - protein **conjugates** with a variety of proteins, such as tetanus toxoid, recombinant human nerve growth factor and insulin was investigated. Sizes ranging from .apprx.100 nm to several μm and protein loading of up to 200% could be attained by changing factors, such as pH, temperature and polymer type. Complex formation was fully reversible. Bioadhesion in a Caco-2 cell culture model and measurable antibody titers in mice using tetanus toxoid - polymer **conjugates** suggest that these polymers could be of interest for protein delivery and mucosal vaccination.
CC 63-5 (Pharmaceuticals)
IT Critical solution temperature
Dissolution
Human
Polymer degradation
(biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)
IT Polyesters, biological studies
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dilactone-based, graft polymerized with vinyl **alc.**; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)
IT Polyethers, biological studies
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(graft polymerized with poly(glycolide-co-lactide); biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)
IT Polymerization
(graft; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)
IT Drug delivery systems
(nanospheres; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)
IT Vaccines
(oral; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)
IT Albumins, biological studies
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(serum, complex with graft copolymers; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)

IT Toxoids
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tetanus, complex with graft copolymers; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)

IT **9002-89-5DP**, Poly(vinyl **alcohol**), butane sultone ethers, reaction products with graft glycolide-lactide copolymer
9004-10-8DP, Insulin, complex with graft copolymers
192646-47-2DP, Glycolide-lactide-vinyl **alcohol** graft copolymer, **conjugates** with proteins
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)

IT 1633-83-6DP, 1,4-Butane sultone, reaction products with poly(vinyl **alc.**) and glycolide-lactide copolymer 192646-47-2P, Glycolide-lactide-vinyl **alcohol** graft copolymer
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)

IT 9007-43-6P, Cytochrome C, biological studies
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(complex with graft copolymers; biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)

IT 26780-50-7P, Glycolide-lactide copolymer
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction products with butane sultone ethers and poly(vinyl **alc.**); biodegradable graft polyesters based on copolymer of lactic acid and glycolic acids grafted onto poly(vinyl **alc.**) for oral vaccine delivery)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:391990 HCAPLUS
DOCUMENT NUMBER: 135:16019
TITLE: Asymmetric hammerhead ribozymes and their diagnostic and therapeutic use
INVENTOR(S): Hendry, Philip; McCall, Maxine J.
PATENT ASSIGNEE(S): Commonwealth Scientific Industrial Research Organization, Australia
SOURCE: U.S., 30 pp., Cont.-in-part of U.S. Ser. No. 627,033, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6238917	B1	20010529	US 1998-156828	19980918
WO 9737013	A1	19971009	WO 1997-AU210	19970402

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	US 1996-627033	B2 19960402
	WO 1997-AU210	A1 19970402
	US 1996-14659P	P 19960402

OTHER SOURCE(S): MARPAT 135:16019

ED Entered STN: 31 May 2001

AB Hammerhead ribozymes that have an asym. loop structure and that have higher than normal cleavage rates are described for use in the control of gene expression by cleavage of a transcript. The ribozyme may be covalently linked to a delivery agent. The invention also includes a composition which comprises the compound in association with an acceptable carrier.

The invention also includes a method of cleaving an RNA target sequence which comprises contacting a target sequence with the compound as described above. Further, a method of treating a disease in man or animals associated with a particular RNA which comprises administrating to the man or animal the compound Further, the invention also includes a diagnostic reagent which comprises the compound Asym. hammerhead ribozymes acting on rat growth hormone mRNA, the Drosophila melanogaster Kruppel gene mRNA, and the HIV-1 tat gene were used to determine the contributions of the loops of the hammerhead ribozyme to the catalytic activity of the ribozyme and sequence requirements were characterized and optimized.

IC ICM A61K031-7088
ICS A61K031-712; C07H021-00; C12N005-10; C12Q001-68

NCL 435325000

CC 7-2 (Enzymes)
Section cross-reference(s): 1, 3, 63

IT Lipids, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic, **conjugates** with ribozyme, as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Peptidomimetics
(**conjugates** with ribozyme, as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Fats and Glyceridic oils, biological studies
Ferritins
Oligosaccharides, biological studies
Peptides, biological studies
Steroids, biological studies
Vitamins
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates** with ribozyme, as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Polyoxyalkylenes, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(**conjugates** with ribozymes, as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Antibodies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates**, with ribozyme, as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Lipoproteins
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-d., **conjugates** with ribozyme, as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT 57-88-5D, **Cholesterol**, **conjugates** with ribozymes
57-88-5D, **Cholesterol**, derivs., **conjugates** with ribozyme 58-85-5D, Biotin, **conjugates** with ribozymes 59-30-3D, Folic acid, **conjugates** with ribozymes 302-79-4D, Retinoic acid, **conjugates** with ribozymes **9004-10-8D**, Insulin, **conjugates** with ribozymes, biological studies **25322-68-3D**, Polyethylene glycol, **conjugates** with ribozymes
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as targeting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:137060 HCAPLUS
DOCUMENT NUMBER: 134:183463
TITLE: The nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers
INVENTOR(S): Park, Myung-Ok; Lee, Kang Choon
PATENT ASSIGNEE(S): S. Korea
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012230	A1	20010222	WO 2000-KR868	20000807
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
KR 2001018158	A	20010305	KR 1999-33984	19990817
EP 1204427	A1	20020515	EP 2000-952020	20000807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507344	T2	20030225	JP 2001-516573	20000807
US 6506730	B1	20030114	US 2000-639483	20000815

PRIORITY APPLN. INFO.: KR 1999-33984 A 19990817
WO 2000-KR868 W 20000807

ED Entered STN: 25 Feb 2001

AB The present invention relates to a pharmaceutical composition for a nasal transmucosal delivery, comprising a biocompatible polymer-biol. active peptide **conjugate.** The pharmaceutical composition of the present invention increases the water solubility of peptide, which is sparingly soluble in water, improves a stability by protecting from being degraded by protease, and, consequently, reduces an administration number of drug to decrease side-effects induced by drug abuse. In addition, since the pharmaceutical composition of the present invention is delivered through the nasal cavity, it allows drug activity to be expressed in a short period of time and improves a bioavailability.

IC ICM A61K047-30

CC 63-5 (Pharmaceuticals)

ST peptide delivery transmucosal nose polymer **conjugate**

IT Polymers, biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(biocompatible; nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT Drug delivery systems
(mucosal; nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT Drug delivery systems
Molecular weight distribution
pH
(nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT Drug delivery systems
(nasal; nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT Polyamides, biological studies
Polyoxyalkylenes, biological studies
Polyphosphazenes
Polysaccharides, biological studies
Polyurethanes, biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(peptide **conjugates**; nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT Enkephalins
Peptides, biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(polymer **conjugates**; nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT 9002-64-6DP, Parathyroid hormone, polymer **conjugates**
9034-40-6DP, Lhrh, polymer **conjugates** 47931-85-1DP, Salmon calcitonin, peptide **conjugates** 57773-63-4DP, Triptorelin, polymer **conjugates** 96352-57-7DP, Glucagon-like peptide, polymer **conjugates**
RL: PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

IT 9002-71-5D, Tsh, polymer **conjugates** **9002-89-5D**, Polyvinyl **alcohol**, peptide **conjugates** 9003-01-4D,

Polyacrylic acid, peptide **conjugates** 9003-05-8D, Polyacrylamide, peptide **conjugates** **9004-10-8D**, Insulin, polymer **conjugates**, biological studies 9004-54-0D, Dextran, peptide **conjugates**, biological studies 9007-12-9D, Calcitonin, polymer **conjugates** 9034-39-3D, Growth hormone-releasing hormone, polymer **conjugates** 25104-18-1D, Poly-L-lysine, peptide **conjugates** **25322-68-3D**, Polyethylene glycol, peptide **conjugates** 25322-69-4D, Polypropylene glycol, peptide **conjugates** 26023-30-3D, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], peptide **conjugates** 26100-51-6D, Polylactic acid, peptide **conjugates** 31714-45-1D, peptide **conjugates** 38000-06-5D, Poly-L-lysine, peptide **conjugates** 63340-72-7D, Thymic humoral factor, polymer **conjugates** 83652-28-2D, Cgrp, polymer **conjugates**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nasal transmucosal delivery of peptides **conjugated** with biocompatible polymers)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:131193 HCAPLUS
DOCUMENT NUMBER: 134:183490
TITLE: Hydrophilic and lipophilic balanced microemulsion formulations of free-form and/or conjugation-stabilized therapeutic agents such as insulin
INVENTOR(S): Ekwuribe, Nnochiri Nkem; Ramaswamy, Muthukumar; Radhakrishnan, Balasingam; Allaudeen, Hameedsulthan S.
PATENT ASSIGNEE(S): Protein Delivery, Inc., USA
SOURCE: U.S., 32 pp., Cont.-in-part of U. S. 5,681,811.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6191105	B1	20010220	US 1997-958383	19971027
US 5359030	A	19941025	US 1993-59701	19930510
US 5438040	A	19950801	US 1994-276890	19940719
US 5681811	A	19971028	US 1995-509422	19950731
US 2003229006	A1	20031211	US 2003-448524	20030530
US 2003229010	A1	20031211	US 2003-448535	20030602
PRIORITY APPLN. INFO.:			US 1993-59701	A3 19930510
			US 1994-276890	A2 19940719
			US 1995-509422	A2 19950731
			US 1997-958383	A3 19971027
			US 2000-614203	A1 20000712

ED Entered STN: 22 Feb 2001
AB A therapeutic formulation comprising a microemulsion of a therapeutic agent in free and/or **conjugate** coupled form, wherein the microemulsion comprises a water-in-oil (w/o) microemulsion including a lipophilic phase and a hydrophilic phase, and has a hydrophilic and lipophilic balance (HLB) value between 3 and 7 is described. The therapeutic agent is selected from the group consisting of insulin, calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, parathyroid hormone, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins,

vasopressin, non-naturally occurring opioids, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminease, adenosine deaminase, RNase, trypsin, chymotrypsin, papain, Ara-A (Arabinofuranosyladenine), acylguanosine, nordeoxyguanosine, azidothymidine, dideoxyadenosine, dideoxycytidine, dideoxyinosine, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, or I-darubicin, erythromycin, vancomycin, oleandomycin, ampicillin, quinidine and heparin. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the insulin, the linear polyalkylene glycol moiety and the lipophilic moiety are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. The microemulsion compns. of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications. For example, a microemulsion formulation was prepared containing Capmul MCM 53.0, Centrophase 31 5.7, propylene glycol 19.9, Tween 80 1.4, hexyl insulin in NaP buffer 15 mg/mL, and NaP buffer up to 100%, resp. Also, preparation of hexyl insulin **conjugates** with Me (ethylene glycol)7-O-hexanoic acid was carried out.

IC ICM A61K038-38
ICS C07K014-62

NCL 514003000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2

ST drug **conjugate** microemulsion stabilization; insulin **conjugate** microemulsion stabilization

IT **Fatty acids**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10, esters with propylene glycol; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Diagnosis
(agents; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates** with tetrahydropyran derivative and insulin; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Antidiabetic agents
Hydrophile-lipophile balance value
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Diglycerides
Enkephalins
Glycerides, biological studies
Hypothalamic hormones
Interferons
Lecithins
Monoglycerides
Opioids
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic and lipophilic balanced microemulsions of free and/or

conjugated drugs such as insulin)

IT Drug delivery systems
(microemulsions; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Surfactants
(nonionic; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Drug delivery systems
(oral; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Drug delivery systems
(parenterals; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT **Alcohols**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT 24167-76-8, Sodium phosphide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buffer; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT 102-82-9, Tri-n-butylamine 3344-77-2, 12-Bromo-1-dodecanol 7075-11-8 7693-46-1, p-Nitrophenylchloroformate 9004-74-4 9005-66-7 9005-70-3 11070-73-8, Bovine insulin 25512-65-6, Dihydropyran 161489-28-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT 7075-11-8DP, tri-Bu derivative 88517-92-4P 100601-63-6P 161756-38-3P 161756-39-4P 212969-35-2P 326892-08-4P 326892-09-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT **9004-95-9DP**, Polyoxyethylene cetyl ether, **conjugates** with tri-Bu AraCMP **9004-99-3DP**, Polyethylene glycol monostearate, **conjugates** with insulin 9005-66-7DP, **conjugates** with insulin 9005-70-3DP, **conjugates** with polysorbate trioleate **11070-73-8DP**, Bovine insulin, **conjugates 25322-68-3DP**, Polyethylene glycol, **conjugates** with tetrahydropyran derivative and insulin 88517-92-4DP, **conjugates** with insulin and polyethylene glycol **212969-35-2DP**, **conjugates** with hexyl insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT 50-44-2, 6-Mercaptopurine 50-91-9, Floxuridine 56-54-2, Quinidine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, esters 69-53-4, Ampicillin 69-65-8, D-Mannitol 114-07-8, Erythromycin 118-00-3D, Guanosine, acyl derivs., biological studies 1404-90-6, Vancomycin 1984-06-1, Sodium octanoate 3922-90-5, Oleandomycin 4097-22-7, Dideoxyadenosine 5536-17-4, Ara-A 7481-89-2, Dideoxycytidine 9000-96-8, Arginase 9001-73-4, Papain 9001-99-4, RNase 9002-07-7, Trypsin 9002-60-2, ACTH, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin

9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies **9004-10-8D**, Insulin, **conjugates** with hexanoic acid derivative, biological studies **9004-10-8D**, Insulin, hexyl polymer **conjugate**, biological studies 9005-49-6, Heparin, biological studies 9005-65-6, Tween 80 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9015-68-3, Asparaginase 9026-93-1, Adenosine deaminase 9027-98-9 9038-70-4, Somatomedin 9054-89-1, Superoxide dismutase 11000-17-2, Vasopressin 11096-26-7, Erythropoietin 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 25322-68-3, Polyethylene glycol 30516-87-1, Azidothymidine 51110-01-1, Somatostatin 58957-92-9, I-Darubicin 60118-07-2, Endorphin 69655-05-6, Dideoxyinosine 82410-32-0 87090-08-2, Labrafil M 1944 120300-18-7, Caprol PGE 860 156259-68-6, Capmul MCM 195739-92-5, Centrophase 31
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin)

IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; hydrophilic and lipophilic balanced microemulsions of free and/or **conjugated** drugs such as insulin but nor protease inhibitor)

IT 8049-47-6, Pancreatin 9001-75-6, Pepsin
RL: CAT (Catalyst use); USES (Uses)
(insulin and its **conjugates** stability in)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:133428 HCAPLUS
DOCUMENT NUMBER: 132:185416
TITLE: Blood-brain barrier therapeutics
INVENTOR(S): Ekwuribe, Nnochiri N.; Radhakrishnan, Balasingam; Price, Christopher H.; Anderson, Wesley R., Jr.; Ausari, Aslam M.
PATENT ASSIGNEE(S): Protein Delivery, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009073	A2	20000224	WO 1999-US18248	19990812
WO 2000009073	A3	20000629		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6703381	B1	20040309	US 1998-134803	19980814
CA 2340418	AA	20000224	CA 1999-2340418	19990812
AU 9956726	A1	20000306	AU 1999-56726	19990812
AU 772494	B2	20040429		
EP 1105142	A2	20010613	EP 1999-943676	19990812

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

BR 9914280	A	20011113	BR 1999-14280		19990812
JP 2002522463	T2	20020723	JP 2000-564577		19990812
US 2004102381	A1	20040527	US 2003-716578		20031119
US 2004110735	A1	20040610	US 2003-716975		20031119
PRIORITY APPLN. INFO.:			US 1998-134803	A	19980814
			WO 1999-US18248	W	19990812

ED Entered STN: 25 Feb 2000

AB The present invention relates to amphiphilic drug-oligomer conjugates capable of traversing the blood-brain barrier and to methods of making and using such conjugates. Amphiphilic drug-oligomer conjugates comprise a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety. The conjugates of the invention further comprise therapeutic agents such as proteins, peptides, nucleosides, nucleotides, antiviral agents, antineoplastic agents, antibiotics, etc., and prodrugs, precursors, derivs. and intermediates thereof, chemical coupled to amphiphilic oligomers. One example conjugate prepared was Met-enkephalin with a succinimidyl triethylene glycol monohexadecyl ester derivative

IC ICM A61K

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 34

IT 9004-10-8DP, **Insulin, conjugates** with polyoxyalkylene derivative, biological studies 259229-23-7DP, conjugates with peptides
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

IT 57-88-5, **Cholesterol**, reactions 111-46-6, reactions 112-27-6, Triethylene glycol 112-82-3 623-65-4, Palmitic anhydride 4484-59-7, Triethylene glycol monohexadecyl ether 6066-82-6, Hydroxysuccinimide 13887-98-4, 3,6,9-Trioxaundecanedioic acid 58569-55-4, Met-enkephalin 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

L17 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:679172 HCAPLUS
DOCUMENT NUMBER: 127:328391
TITLE: Asymmetric hammerhead ribozymes and their diagnostic and therapeutic use
INVENTOR(S): Hendry, Philip; McCall, Maxine J.
PATENT ASSIGNEE(S): Commonwealth Scientific and Industrial Research Organisation, Australia; Hendry, Philip; McCall, Maxine J.
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9737013	A1	19971009	WO 1997-AU210	19970402

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,

PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2250857	AA	19971009	CA 1997-2250857		19970402
AU 9721450	A1	19971022	AU 1997-21450		19970402
AU 721758	B2	20000713			
EP 902836	A1	19990324	EP 1997-913997		19970402
R: DE, FR, GB, IT					
JP 2000509969	T2	20000808	JP 1997-534751		19970402
US 6238917	B1	20010529	US 1998-156828		19980918
PRIORITY APPLN. INFO.:			US 1996-14659P	P	19960402
			US 1996-627033	A2	19960402
			WO 1997-AU210	W	19970402

ED Entered STN: 25 Oct 1997

AB Hammerhead ribozymes that have an asym. loop structure and that have higher than normal cleavage rates are described for use in the control of gene expression by cleavage of a transcript. The ribozyme can also be used to detect its substrate and so may be of diagnostic use. The ribozyme may be of therapeutic use and can be delivered to a target tissue as a **conjugate** with a targetting or delivery agent. Modifications that can increase the stability or activity of the ribozyme are extensively listed. Asym. hammerhead ribozymes acting on rat growth hormone mRNA, the Drosophila melanogaster Krueppel gene mRNA, and the HIV-1 tat gene were used to determine the contributions of the loops of the hammerhead ribozyme to the catalytic activity of the ribozyme and sequence requirements characterized and optimized.

IC ICM C12N015-11
ICS A61K031-70

CC 7-2 (Enzymes)
Section cross-reference(s): 1, 3, 9

IT Lipids, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cationic, **conjugates** with ribozymes, as targetting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Antibodies
Carbohydrates, biological studies
Ferritins
Oligosaccharides, biological studies
Peptides, biological studies
Peptidomimetics
Steroids, biological studies
Vitamins
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates** with ribozymes, as targetting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Polyoxyalkylenes, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs., **conjugates** with ribozymes, as targetting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Coenzymes
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(folate, **conjugates** with ribozymes, as targetting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT Lipoproteins

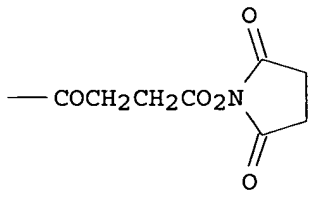
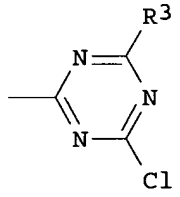
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-d., **conjugates** with ribozymes, as targetting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

IT 57-88-5D, **Cholesterol**, derivs., **conjugates** with ribozymes 58-85-5D, Biotin, **conjugates** with ribozymes 302-79-4D, Retinoic acid, derivs., **conjugates** with ribozymes **9004-10-8D**, Insulin, derivs., **conjugates** with ribozymes, biological studies **25322-68-3D**, derivs., **conjugates** with ribozymes
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as targetting moiety; asym. hammerhead ribozymes and their diagnostic and therapeutic use)

L17 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:181545 HCAPLUS
DOCUMENT NUMBER: 124:233169
TITLE: Preparation of protein or polypeptide **conjugate** with polyethylene glycol **cholesterol** ether and intermediate compound therefor
INVENTOR(S): Suzuki, Yosuke; Sato, Syuji
PATENT ASSIGNEE(S): Hisamitsu Pharmaceutical Co., Inc., Japan
SOURCE: PCT Int. Appl., 32 pp
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9532219	A1	19951130	WO 1995-JP968		19950519
W: AU, CA, CN, JP, KR, US, VN					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU 9524552	A1	19951218	AU 1995-24552		19950519
EP 761683	A1	19970312	EP 1995-918754		19950519
EP 761683	B1	20050202			
R: CH, DE, ES, FR, GB, IE, IT, LI, NL, SE					
JP 3173794	B2	20010604	JP 1995-529927		19950519
US 5889153	A	19990330	US 1997-737820		19970314
PRIORITY APPLN. INFO.:			JP 1994-107301	A	19940520
			WO 1995-JP968	W	19950519

ED Entered STN: 29 Mar 1996
GI

Q=  Q1= 

AB A protein or polypeptide having at least one amino group bonded to a polyethylene glycol group represented by the following general formula

R1(OCH2CH2)nO (wherein R1 = optionally substituted cholesteryl; n = a pos. integer which is arbitrarily variable) is prepared using a reactive polyethylene glycol derivative R1(OCH2CH2)nOR2 [I; R2 = CO2C6H4NO2-p, Q, Q1; wherein R3 = OH, alkoxy, acyloxy, halo, R1 (O CH2CH2)nO; n = same as above]. The obtained chemical modified protein or polypeptide does not cause receptor coupling inhibition and has a high physiol. activity, improved in vivo behaviors, improved water solubility, increased storage stability, reduced antigenic activity, and enzyme resistance, and makes it possible to develop an oral or nonoral drug having a high pharmacol. effect. Thus, esterification of polyethylene glycol monocholesteryl ether (n = 20, average mol. weight 1,200) with succinic anhydride in CH2Cl2 containing pyridine under reflux gave polyethylene glycol monocholesteryl ether succinic acid ester I (R1 = same as above, R2 = COCH2CH2CO2H), which was esterified with N-hydroxysuccinimide using DCC in DMF at room temperature for 24 h to give 78% the succinimide ester I (R1 = same as above; R2 = Q). The latter active ester (2.0) nmol was added to a solution of 6.0 mg bovine insulin in 0.025 mM Na2B4O7.10H2O (pH 9.2) and stirred at room temperature for 5 h to give, after gel filtration purification using Sephadex D-75, insulin modified with one or two cholesterylpoly(ethylene glycol). This insulin **conjugate** in vitro interacted with serum components other than albumin and in vivo the modification did not hinder the interaction with insulin receptor. It is useful for treatment and prevention of diabetes. Also prepared was cholesterylpoly(ethylene glycol)-modified superoxide dismutase (SOD), which is useful as an antiulcer and antiinflammatory agent.

IC ICM C07K014-00
ICS A61K038-28; A61K038-44; C08G065-32

CC 34-4 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST polypeptide **conjugate** polyethylene glycol prepn; protein **conjugate** polyethylene glycol prepn; polyethylene glycol **cholesterol** ether **conjugate** protein; antiulcer polypeptide **conjugate** polyethylene glycol; antiinflammatory polypeptide **conjugate** polyethylene glycol; diabetes treatment polypeptide **conjugate** polyethylene glycol

IT Peptides, preparation
Proteins, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of protein or polypeptide **conjugate** with polyethylene glycol **cholesterol** ether as drugs)

IT **9004-10-8DP**, Insulin, **conjugate** with O-cholesterylpoly(ethylene glycol)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antidiabetic; preparation of O-cholesterylpoly(ethylene glycol)-peptides or proteins as drugs)

IT 9054-89-1D, **Conjugate** with PEG
RL: RCT (Reactant); RACT (Reactant or reagent)
(copper, zinc containing; preparation of O-cholesterylpoly(ethylene glycol)-peptides or proteins as drugs)

IT **25322-68-3DP**, **conjugate** with bovine superoxide dismutase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of O-cholesterylpoly(ethylene glycol)-peptides or proteins as drugs)

L17 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:76627 HCAPLUS
DOCUMENT NUMBER: 118:76627
TITLE: Hydrazine-containing **conjugates** of polypeptides and glycopolypeptides with polymers
INVENTOR(S): Zalipsky, Samuel; Lee, Chyi; Menon-Rudolph, Sunitha
PATENT ASSIGNEE(S): Enzon, Inc., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9216555	A1	19921001	WO 1992-US2047	19920312
W: AU, CA, HU, JP, KR, RU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
AU 9216769	A1	19921021	AU 1992-16769	19920312
EP 576589	A1	19940105	EP 1992-909326	19920312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06506217	T2	19940714	JP 1992-508914	19920312
CA 2101918	AA	19920919	CA 1992-2101918	19920316
PRIORITY APPLN. INFO.:			US 1991-672696 A	19910318
			WO 1992-US2047 A	19920312

ED Entered STN: 02 Mar 1993

AB Biol. active polypeptides and glycopolypeptides are **conjugated** at a reactive carbonyl or carboxylic acid group of the polypeptide with water-soluble polymers by a linkage containing a hydrazide or hydrazone functional group. The linkage preferably also includes an amino acid or peptide sequence. The **conjugates** represent a novel form of drug delivery (no data). Methoxy-PEG (mPEG) was treated with phosgene and then reacted with β-alanine Et ester.HCl. The mPEG-β-alanine Et ester product was treated with hydrazine under reflux for 6 h and the mPEG-hydrazide derivative containing β-Ala was **conjugated** to various proteins, e.g. activated chymotrypsin, activated bovine serum albumin, oxidized ovalbumin, oxidized human IgG, and activated G-CSF. The proteins were activated at the carboxyl groups with EDC (carbodiimide) or N-hydroxy-5-norbornene-2,3-dicarboximide. Carbohydrate groups were oxidized with NaIO4 for activation. Extensive crosslinking of the proteins was prevented.

IC ICM C07K007-26
ICS C07K007-34; C07K007-40; C07K015-14; C07K015-26; C07K015-28; C07K017-08; C07K017-10; C08F016-08; C08F020-18; C08F026-10; C08L029-04; C08L033-26; C08L039-06; C08L057-10; C12N009-14; C12N009-68; C12N009-76; C12N009-82; C12N009-96

CC 9-14 (Biochemical Methods)
Section cross-reference(s): 63

ST protein **conjugate** polymer hydrazide hydrazone; glycoprotein **conjugate** polymer hydrazide hydrazone; hydrazine protein glycoprotein **conjugate** polymer

IT Antidiuretics
Pigments, biological
(hormones, **conjugates** with water-soluble polymers, hydrazide or hydrazone linkage in)

IT Hydrazides
Hydrazones
RL: ANST (Analytical study)
(linkage containing, between **conjugate** of glycopolypeptide or polypeptide and water-soluble polymer)

IT Amino acids, biological studies
RL: BIOL (Biological study)
(linkages containing hydrazide or hydrazone and, in glycopolypeptide or polypeptide **conjugates** with water-soluble polymers)
IT Ovalbumins
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidation of, with sodium periodate, in preparation of **conjugates** with methoxylated PEG)
IT Immunoglobulins
RL: ANST (Analytical study)
(A, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT Immunoglobulins
RL: ANST (Analytical study)
(D, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT Immunoglobulins
RL: ANST (Analytical study)
(E, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT Immunoglobulins
RL: RCT (Reactant); RACT (Reactant or reagent)
(G, oxidation of, with sodium periodate, in preparation of **conjugates** with methoxylated PEG)
IT Immunoglobulins
RL: ANST (Analytical study)
(G, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT Immunoglobulins
RL: ANST (Analytical study)
(M, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT Polymers, compounds
Polyoxyalkylenes, compounds
RL: ANST (Analytical study)
(**conjugates**, with glycopolypeptide or polypeptide, hydrazide or hydrazone linkage in)
IT Albumins, compounds
RL: ANST (Analytical study)
(**conjugates**, with methoxylated PEG, hydrazide and β-alanine in linkage of)
IT Agglutinins and Lectins
Enzymes
Glycopeptides
Glycoproteins, specific or class
Hormones
Immunoglobulins
Interferons
Ovalbumins
Peptides, compounds
Proteins, specific or class
RL: ANST (Analytical study)
(**conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT Lymphokines and Cytokines
RL: ANST (Analytical study)
(interleukins, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)
IT **Alcohols**, compounds
RL: ANST (Analytical study)

(polyhydric, ethoxylated, **conjugates**, with glycopolypeptide or polypeptide, hydrazide or hydrazone linkage in)

IT Hypothalamic hormones
RL: ANST (Analytical study)
(releasing, **conjugates**, with water-soluble polymers, hydrazide or hydrazone linkage in)

IT 50-70-4D, D-Glucitol, polyoxyethylenated derivs., **conjugates** with glycopolypeptide or polypeptide 50-99-7D, D-Glucose, polyoxyethylenated derivs., **conjugates** with glycopolypeptide or polypeptide 56-81-5D, 1,2,3-Propanetriol, polyoxyethylenated derivs., **conjugates** with glycopolypeptide or polypeptide 9000-96-8D, Arginase, **conjugates** with water-soluble polymers 9001-05-2D, Catalase, **conjugates** with water-soluble polymers 9001-27-8D, Blood-coagulation factor VIII, **conjugates** with water-soluble polymers 9001-34-7D, Galactosidase, **conjugates** with water-soluble polymers 9001-37-0D, Glucose oxidase, **conjugates** with water-soluble polymers 9001-45-0D, Glucuronidase, **conjugates** with water-soluble polymers 9001-62-1D, Lipase, **conjugates** with water-soluble polymers 9002-12-4D, Uricase, **conjugates** with water-soluble polymers 9002-60-2D, ACTH, **conjugates** with water-soluble polymers 9002-62-4D, Prolactin, **conjugates** with water-soluble polymers 9002-64-6D, Parathyroid hormone, **conjugates** with water-soluble polymers 9002-67-9D, Luteinizing hormone, **conjugates** with water-soluble polymers 9002-72-6D, Somatotropin, derivs., **conjugates** with water-soluble polymers **9002-89-5D**, Polyvinyl **alcohol**, **conjugates** with glycopolypeptide or polypeptide 9003-39-8D, Polyvinyl pyrrolidone, **conjugates** with glycopolypeptide or polypeptide 9004-07-3D, Chymotrypsin, **conjugates** with water-soluble polymers **9004-10-8D**, Insulin, **conjugates** with water-soluble polymers 9004-54-0D, Dextran, **conjugates** with glycopolypeptide or polypeptide **9004-74-4D**, **conjugates** with glycopolypeptide or polypeptide 9007-92-5D, Glucagon, **conjugates** with water-soluble polymers 9015-68-3D, Asparaginase, **conjugates** with water-soluble polymers 9026-93-1D, Adenosine deaminase, **conjugates** with water-soluble polymers 9033-06-1D, Glucosidase, **conjugates** with water-soluble polymers 9033-10-7D, **conjugates** with water-soluble polymers 9038-70-4D, Somatomedin, derivs., **conjugates** with water-soluble polymers 9054-89-1D, Superoxide dismutase, **conjugates** with water-soluble polymers 11096-26-7D, Erythropoietin, **conjugates** with water-soluble polymers **25322-68-3D**, **conjugates** with glycopolypeptide or polypeptide 37228-64-1D, Glucocerebrosidase, **conjugates** with water-soluble polymers 51110-01-1D, Somatostatin, **conjugates** with water-soluble polymers 61512-21-8D, Thymosin, **conjugates** with water-soluble polymers 62683-29-8D, Colony-stimulating factor, derivs., **conjugates** with water-soluble polymers 80619-01-8D, Bilirubin oxidase, **conjugates** with water-soluble polymers **106392-12-5D**, **conjugates** with glycopolypeptide or polypeptide 139639-23-9D, Tissue plasminogen activator, **conjugates** with water-soluble polymers
RL: ANST (Analytical study)
(hydrazide or hydrazone linkage in)

IT 143011-72-7D, G-CSF, **conjugates** with methoxylated PEG
RL: ANST (Analytical study)
(linkage containing hydrazide and β-alanine in)

IT 60-32-2 107-95-9, β-Alanine 327-57-1, Norleucine 672-15-1, Homoserine 2835-81-6, α-Amino butyric acid 56-12-2, biological studies
RL: ANST (Analytical study)
(linkages containing hydrazide or hydrazone and, in glycopolypeptide or

polypeptide **conjugates** with water-soluble polymers)
IT 21032-84-8DP, methoxylated PEG-alanine **conjugates** reaction products
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with activated glycoproteins and proteins)
IT 924-73-2DP, β-Alanine ethyl ester, methoxylated PEG **conjugates**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with hydrazine)
IT 302-01-2, Hydrazine, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with methoxylated PEG-alanine Et ester **conjugate**
)

L17 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:542250 HCAPLUS
DOCUMENT NUMBER: 115:142250
TITLE: Boronic acid-containing polymer complexes for treatment of sugar-related diseases
INVENTOR(S): Miyazaki, Tsuyoshi; Murata, Yoshishige; Shiino, Daijiro; Waki, Kazunori; Sakurai, Yasuhisa; Okano, Teruo; Kataoka, Kazunori; Koyama, Yoshiyuki; Yokoyama, Masayuki; Kitano, Shigeru
PATENT ASSIGNEE(S): Nippon Oil and Fats Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 424168	A1	19910424	EP 1990-311485		19901019
EP 424168	B1	19930901			
R: BE, CH, DE, DK, FR, GB, IT, LI, NL, SE					
JP 04124145	A2	19920424	JP 1990-241191		19900913
JP 2874309	B2	19990324			
JP 04124144	A2	19920424	JP 1990-241192		19900913
JP 3087293	B2	20000911			
JP 2000086534	A2	20000328	JP 1999-297752		19900913
JP 03204823	A2	19910906	JP 1990-275441		19901016
JP 3018463	B2	20000313			
CA 2027930	AA	19910420	CA 1990-2027930		19901018
CA 2027930	C	19980630			
AU 9064754	A1	19910711	AU 1990-64754		19901018
AU 628674	B2	19920917			
US 5478575	A	19951226	US 1993-37383		19930326
PRIORITY APPLN. INFO.:			JP 1989-270215	A	19891019
			JP 1990-241191	A	19900913
			JP 1990-241192	A	19900913
			US 1990-599718	B1	19901019

ED Entered STN: 05 Oct 1991
AB A polymer complex of a sugar response type comprises boronic acid groups linked to medicines containing hydroxy groups. The complex may also comprise polymers having boronic acid groups and polymers having hydroxy groups which are crossedlinked. Matrex PBA-30 (benzeneboronic acid-crosslinked agarose gel) was treated with glucosylated insulin to give an agent for

treatment of diabetes.
IC ICM A61K047-32
ICS A61K047-48
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 38
ST boronate polymer insulin **conjugate** antidiabetic
IT Corticosteroids, compounds
RL: BIOL (Biological study)
(**conjugates**, with aminobenzenboronic acid-containing polymers)
IT 7683-59-2DP, Isoproterenol, **conjugates** with aminobenzenboronic acid-containing polymers. **9004-10-8DP**, Insulin, derivs., **conjugates** with aminobenzeneboronic acid-containing polymers **11070-73-8DP**, Insulin (ox), reaction products with aminobenzeneboronic acid-containing polymers 11111-23-2DP, Lividomycin, **conjugates** with aminobenzenboronic acid-containing polymers. 106956-31-4DP, Matrex Gel PBA 30, reaction products with insulin 136043-29-3DP, **conjugates** with isoproterenol 136043-30-6DP, **conjugates** with insulin derivs. **136043-35-1DP**, reaction products with insulin 136161-94-9DP, **conjugates** with insulin derivs.
RL: PREP (Preparation)
(preparation of, for treatment of sugar-related diseases)
IT 57-92-1D, Streptomycin, **conjugates** with aminobenzeneboronic acid-containing polymers 59-01-8D, Kanamycin, **conjugates** with aminobenzeneboronic acid-containing polymers 530-08-5D, **conjugates** with aminobenzeneboronic acid-containing polymers 536-24-3D, Butanefrine, **conjugates** with aminobenzeneboronic acid-containing polymers 8063-07-8D, Kanamycin, **conjugates** with aminobenzeneboronic acid-containing polymers **9002-89-5D**, Poly(vinyl **alcohol**), **conjugates** with aminobenzenboronic acid-containing polymers and hydroxy-containing medicines 9004-54-0D, Dextran, **conjugates** with aminobenzenboronic acid-containing polymers and hydroxy-containing medicines 9005-82-7D, Amylose, **conjugates** with aminobenzenboronic acid-containing polymers and hydroxy-containing medicines 9007-92-5D, Glucagon, **conjugates** with aminobenzeneboronic acid-containing polymers 9057-02-7D, Pullulan, **conjugates** with aminobenzenboronic acid-containing polymers and hydroxy-containing medicines 11078-30-1D, Galactomannan, **conjugates** with aminobenzenboronic acid-containing polymers and hydroxy-containing medicines 18559-59-6D, Trimethoquinol, **conjugates** with aminobenzeneboronic acid-containing polymers 26279-88-9D, **conjugates** with aminobenzeneboronic acid-containing polymers 51110-01-1D, Somatostatin, **conjugates** with aminobenzeneboronic acid-containing polymers
RL: BIOL (Biological study)
(sugar-related diseases treatment with)

L17 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:21146 HCAPLUS
DOCUMENT NUMBER: 112:21146
TITLE: Preparation of cyclotriphosphazene derivatives bound to hydrophilic polymer and therapeutic physiologically active substance
INVENTOR(S): Suzuki, Yoshiki; Nawata, Kyoshi; Makino, Juji
PATENT ASSIGNEE(S): Teijin Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

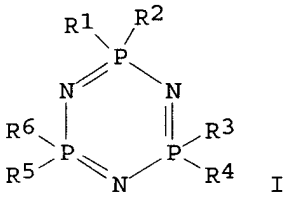
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01175999	A2	19890712	JP 1987-330218	19871228
JP 07051592	B4	19950605		

PRIORITY APPLN. INFO.: JP 1987-330218 19871228

ED Entered STN: 21 Jan 1990

GI



I

AB Cyclotriphosphazene derivs. [I; ≥1 of R1-R6 = hydrophilic polymer or its derivative such as polyethylene glycol, monomethoxypolyethylene glycol, polypropylene glycol, copolymer of ethylene oxide and propylene oxide, dextran, insulin, pullulan, chondroitin, etc.; ≥1 of the other R1-R6 = therapeutic physiol. active substance or its derivative containing 1 or ≥2 groups selected from OH, NH2, NH, or SH such as peptide hormones (insulin, calcitonin, and natriuretic peptide), enzymes (superoxide dismutase, asparaginase, and bilirubin oxidase), proteins (Hb, TPA, and interferon), anticancer agents (mitomycin C, daunorubicin, and doxorubicin), and steroids (estradiol 3-Me ether, testosterone, and triamcinolone acetonide); when the number of the above substituents is ≤5, the rest of R1-R6 = 1 or ≥2 of OR7, NHR8, NR9R10, C1-24 alkyl, or halo; OR7 = tyrosine residue, C1-24 alkoxy; NHR8 = amino acid residue or C1-24 alkylamino; R9, R10 = C1-24 alkyl] which impart the therapeutic physiol. active substance such advantages as the increased bioavailability, prolonged half-life, reduced side-effect such as antigenicity, enhanced delivery to diseased sites, and high safety margin, are prepared Thus, treatment of monomethoxypolyethylene glycol (II) with NaH in THF to give the Na **alcoholate** followed by reaction with hexachlorocyclotriphosphazene in THF gave II-cyclotriphosphazene which was reacted with glycine Et ester (III) to give, after purification by gel filtration, II, III-cyclotriphosphazene (IV) containing 1 Cl for each cyclotriphosphazene ring. The latter compound (1.5 g) and 15 mg superoxide dismutase (V) were allowed to react 2 h at 4° in 5 mL 0.1M phosphate buffer (pH 9.0) and diluted with 0.1M phosphate buffer (pH 7.0) to give, after removal of unreacted IV by ultrafiltration and purification by gel filtration, 15 mg II, III-cyclotriphosphazene-V containing 1 II, 1 V, and 4 III. This V derivative retained .apprx.70% of V activity, showed the serum half-life of 15.2 h vs. that of 1.6 h for V, did not produce antibody due to passive anaphylaxis reaction in mice, and increased the absorption through duodenum in rats. Also prepared were II, III-cyclotriphosphazene bound to insulin, asparaginase, mitomycin C, doxorubicin, daunomycin, and estradiol 3-Me ether.

IC ICM C07K015-12
ICS A61K031-40; A61K031-565; A61K031-71; A61K031-715; A61K031-725; A61K031-77; A61K031-785; A61K031-80; A61K037-02; A61K037-24; A61K037-48; A61K047-00; C07K007-40; C07K015-22; C07K017-08;

C07K017-10; C08B015-06; C08B031-00; C08B037-00
CC 29-7 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 1
IT Neoplasm inhibitors
(cyclotriphosphazene derivs. **conjugates**)
IT Enzymes
Interferons
RL: SPN (Synthetic preparation); PREP (Preparation)
(hydrophilic polymer-cyclotriphosphazene derivs. **conjugates** with, preparation and improved biol. properties of)
IT Hemoglobins
RL: SPN (Synthetic preparation); PREP (Preparation)
(**conjugates**, with cyclotriphosphazene derivs., preparation and improved biol. properties of)
IT 940-71-6DP, reaction products with monomethoxypolyethylene glycol and pharmaceuticals 9004-54-0DP, Dextran, reaction products with hexachlorocyclotriphosphazene and pharmaceuticals **9004-74-4DP**, Monomethoxypolyethyleneglycol, reaction products with hexachlorocyclotriphosphazene and pharmaceuticals
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and biol. activity of)
IT 50-07-7DP, Mitomycin C, cyclotriphosphazene derivative **conjugates** 58-22-0DP, Testosterone, cyclotriphosphazene derivative **conjugates** 76-25-5DP, Triamcinolone acetonide, cyclotriphosphazene derivative **conjugates** 1035-77-4DP, Estradiol 3-methyl ether, cyclotriphosphazene derivative **conjugates** **9004-10-8DP**, Insulin, cyclotriphosphazene derivative **conjugates** 9007-12-9DP, Calcitonin, cyclotriphosphazene derivative **conjugates** 9015-68-3DP, Asparaginase, cyclotriphosphazene derivative **conjugates** 9054-89-1DP, Superoxide dismutase, cyclotriphosphazene derivative **conjugates** 20830-81-3DP, Daunorubicin, cyclotriphosphazene derivative **conjugates** 21062-37-3DP, cyclotriphosphazene derivative **conjugates** 23214-92-8DP, Doxorubicin, cyclotriphosphazene derivative **conjugates** 80619-01-8DP, Bilirubin oxidase, cyclotriphosphazene derivative **conjugates** 85637-73-6DP, Atriopeptin, cyclotriphosphazene derivative **conjugates**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and improved biol. properties of)

L17 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1980:185910 HCAPLUS
DOCUMENT NUMBER: 92:185910
TITLE: Nonimmunogenic polypeptides
INVENTOR(S): Davis, Frank F.; Van Es, Theodorus; Palczuk, Nicholas C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 12 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4179337	A	19791218	US 1977-819831	19770728
PRIORITY APPLN. INFO.:			US 1973-381191 A2	19730720
			US 1975-596931 A2	19750717

ED Entered STN: 12 May 1984
AB Polypeptides such as enzymes or insulin are coupled to polyethylene glycol (PEG) or polypropylene glycol to give a phys. active nonimmunogenic water for polypeptide composition The glycols protect the peptides from loss of activity and the composition can be injected with no immunogenic response. Thus, PEG 750 [25322-68-3] or PEG 2000 was dissolved in anhydrous C6H6 containing Na2CO3. The solution was cooled and cyanuric chloride [108-77-0] was
added to give PEG 4-hydroxy-6-chloro-1,3,5-triazine (I) [58914-58-2]. I was added to insulin, dissolved in 0.1 M borate buffer, pH 9.2, to give a PEG-4-hydroxy-1,3,5-triazin-6-yl **conjugate** (II). II had insulin activity of .apprx.50% of insulin activity when injected into rabbits based on weight of **conjugated** insulin administered. II also had no antigenic activity visavis insulin antiserum.
IC C07G007-00; C07G007-02; A61K037-26; A61K037-48
NCL 435181000
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 7
ST polyalkylene glycol insulin **conjugate**; nonimmunogenic polypeptide **conjugate**; enzyme polyalkylene glycol **conjugate**
IT 58914-60-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with **cholesterol** hydroxylation)
IT **73348-31-9DP**, reaction products with insulin
RL: PREP (Preparation)
(preparation of, for nonimmunogenic polypeptides)
IT 9001-63-2DP, reaction products with azidonitrophenyl polyethylene glycol
9002-07-7DP, reaction products with aminopolyethylene glycol
9004-10-8DP, reaction products with polyethylene glycol derivs.
RL: PREP (Preparation)
(preparation of, for nonimmunogenic prepns.)

=>